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<p>(21) International Application Number: PCT/EP00/02450</p> <p>(22) International Filing Date: 20 March 2000 (20.03.00)</p> <p>(30) Priority Data:</p> <table border="0"> <tr> <td>60/126,707</td> <td>29 March 1999 (29.03.99)</td> <td>US</td> </tr> <tr> <td>60/165,948</td> <td>17 November 1999 (17.11.99)</td> <td>US</td> </tr> <tr> <td>60/165,944</td> <td>17 November 1999 (17.11.99)</td> <td>US</td> </tr> </table> <p>(71) Applicant: F. HOFFMANN-LA ROCHE AG [CH/CH]; Grenzacherstrasse 124, CH-4070 Basle (CH).</p>		60/126,707	29 March 1999 (29.03.99)	US	60/165,948	17 November 1999 (17.11.99)	US	60/165,944	17 November 1999 (17.11.99)	US	<p>(72) Inventors: BIZZARRO, Fred, Thomas; 85 Sterling Drive, Colonia, NJ 07067 (US). CORBETT, Wendy, Lea; 36 Ridgewood Drive, Randolph, NJ 07869-3754 (US). FOCELLA, Antonino; 61 Warner Way, Wayne, NJ 07470 (US). GRIPPO, Joseph, Francis; 324 Somerset Street #7, Stirling, NJ 07980 (US). HAYNES, Nancy-Ellen; 508 Linden Place, Cranford, NJ 07016 (US). HOLLAND, George, William; 10 Acorn Place, North Caldwell, NJ 07006 (US). KESTER, Robert, Francis; Apartment 438, 240 Prospect Avenue, Hackensack, NJ 07601 (US). MAHANEY, Paige, E.; Apartment 1A, 828 Bloomfield Avenue, Montclair, NJ 07042 (US). SARABU, Ramakanth; 73 Forest Road, Cedar Grove, NJ 07009 (US).</p> <p>(74) Agent: WITTE, Hubert; Grenzacherstrasse 124, CH-4070 Basle (CH).</p> <p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published Without international search report and to be republished upon receipt of that report.</p>
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<p>(54) Title: GLUCOKINASE ACTIVATORS</p> <div style="text-align: center;"> <p>(I)</p> </div> <p>(57) Abstract</p> <p>The present invention relates to compounds of formula (I) wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are as defined in claim 1 and pharmaceutically acceptable salts thereof. The compounds are glucokinase activators which increase insulin secretion in the treatment of type II diabetes.</p>											

### Glucokinase activators

Glucokinase (GK) is one of four hexokinases that are found in mammals [Colowick, S.P., in *The Enzymes*, Vol. 9 (P. Boyer, ed.) Academic Press, New York, NY, pages 1-48, 1973]. The hexokinases catalyze the first step in the metabolism of glucose, i.e., the conversion of glucose to glucose-6-phosphate. Glucokinase has a limited cellular  
5 distribution, being found principally in pancreatic  $\beta$ -cells and liver parenchymal cells. In addition, GK is a rate-controlling enzyme for glucose metabolism in these two cell types that are known to play critical roles in whole-body glucose homeostasis [Chipkin, S.R., Kelly, K.L., and Ruderman, N.B. in *Joslin's Diabetes* (C.R. Khan and G.C. Wier, eds.), Lea and Febiger, Philadelphia, PA, pages 97-115, 1994]. The concentration of glucose at  
10 which GK demonstrates half-maximal activity is approximately 8 mM. The other three hexokinases are saturated with glucose at much lower concentrations (<1 mM). Therefore, the flux of glucose through the GK pathway rises as the concentration of glucose in the blood increases from fasting (5 mM) to postprandial ( $\approx$ 10-15 mM) levels following a carbohydrate-containing meal [Printz, R.G., Magnuson, M.A., and Granner,  
15 D.K. in *Ann. Rev. Nutrition* Vol. 13 (R.E. Olson, D.M. Bier, and D.B. McCormick, eds.), Annual Review, Inc., Palo Alto, CA, pages 463-496, 1993]. These findings contributed over a decade ago to the hypothesis that GK functions as a glucose sensor in  $\beta$ -cells and hepatocytes (Meglasson, M.D. and Matschinsky, F.M. *Amer. J. Physiol.* **246**, E1-E13, 1984). In recent years, studies in transgenic animals have confirmed that GK does indeed  
20 play a critical role in whole-body glucose homeostasis. Animals that do not express GK die within days of birth with severe diabetes while animals overexpressing GK have improved glucose tolerance (Grupe, A., Hultgren, B., Ryan, A. et al., *Cell* **83**, 69-78, 1995; Ferrie, T., Riu, E., Bosch, F. et al., *FASEB J.*, **10**, 1213-1218, 1996). An increase in glucose exposure is coupled through GK in  $\beta$ -cells to increased insulin secretion and in  
25 hepatocytes to increased glycogen deposition and perhaps decreased glucose production.

- $R^4$  is  $-C(O)NHR^{40}$ , or an unsubstituted or mono-substituted five- or six-membered heteroaromatic ring connected by a ring carbon atom to the amine group shown, which five- or six-membered heteroaromatic ring contains from 1 to 3 heteroatoms selected from sulfur, oxygen or nitrogen, with one heteroatom being nitrogen which is adjacent to the connecting ring carbon atom; said mono-substituted heteroaromatic ring being monosubstituted at a position on a ring carbon atom other than adjacent to said connecting carbon atom with a substituent selected from the group consisting of lower alkyl, halo, nitro, cyano,  $-(CH_2)_n-OR^6$ ,  $-(CH_2)_n-C(O)OR^7$ ,  $-(CH_2)_n-C(O)NHR^6$ ,  $-C(O)-C(O)OR^8$ ,  $-(CH_2)_n-NHR^6$ ;
- $R^{40}$  is hydrogen, lower alkyl, lower alkenyl, hydroxy lower alkyl, halo lower alkyl,  $-(CH_2)_n-C(O)OR^5$  or  $-C(O)-(CH_2)_n-C(O)OR^6$ ;
- $R^5$  is hydrogen, lower alkyl or perfluoro-lower alkyl;
- $R^6$ ,  $R^7$  and  $R^8$  are independently hydrogen or lower alkyl; and
- $n$  is 0, 1, 2, 3 or 4;
- or a pharmaceutically acceptable salt thereof.

In the compound of formula I, the \* indicates the asymmetric carbon atom in this compound. The compound of formula I may be present either as a racemate or in the "R" configuration at the asymmetric carbon shown. The "R" enantiomers are preferred.

The compounds of formula I have been found to activate glucokinase *in vitro*. Glucokinase activators are useful for increasing insulin secretion in the treatment of type II diabetes.

The present invention also relates to a pharmaceutical composition comprising a compound of formula I and a pharmaceutically acceptable carrier and/or adjuvant. Furthermore the present invention relates to the use of such compounds for the

As used herein, "lower alkyl sulfinyl" means a lower alkyl group as defined above where a sulfinyl group is bound to the rest of the molecule.

As used herein, "hydroxyamino" designates an amino group where one of the hydrogens is replaced by a hydroxy.

5       As used herein, "cycloalkyl" means a saturated hydrocarbon ring having from 3 to 10 carbon atoms, preferably from 3 to 7 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc. A preferred cycloalkyl is cyclopentyl.

As used herein, the term "lower alkenyl" denotes an alkylene group having from 2 to 6 carbon atoms with a double bond located between any two adjacent carbons of the  
10       group. Preferred lower alkenyl groups are allyl and crotyl.

As used herein, the term "lower alkoxy" includes both straight chain and branched chain alkoxy groups having from 1 to 7 carbon atoms, such as methoxy, ethoxy, propoxy, isopropoxy, preferably methoxy and ethoxy.

As used herein, the term "aryl" signifies aryl mononuclear aromatic hydrocarbon  
15       groups such as phenyl, tolyl, etc. which can be unsubstituted or substituted in one or more positions with halogen, nitro, lower alkyl, or lower alkoxy substituents and polynuclear aryl groups, such as naphthyl, anthryl, and phenanthryl, which can be unsubstituted or substituted with one or more of the aforementioned groups. Preferred aryl groups are the substituted and unsubstituted mononuclear aryl groups, particularly phenyl. The term  
20       "arylalkyl" denotes an alkyl group, preferably lower alkyl, in which one of the hydrogen atoms is replaced by an aryl group. Examples of arylalkyl groups are benzyl, 2-phenylethyl, 3-phenylpropyl, 4-chlorobenzyl, 4-methoxybenzyl and the like.

As used herein, the term "lower alkanoic acid" denotes lower alkanoic acids containing from 2 to 7 carbon atoms such as propionic acid, acetic acid and the like. The  
25       term "lower alkanoyl" denotes monovalent alkanoyl groups having from 2 to 7 carbon atoms such as propionoyl, acetyl and the like. The term "aroic acids" denotes aryl alkanoic acids where aryl is as defined above and alkanoic contains from 1 to 6 carbon atoms. The term "aroyl" denotes aroic acids wherein aryl is as defined hereinbefore, with



dicarboxycyclic acid. Among the activated acids which can be utilized to form such groups are acid anhydrides, acid halides, preferably acid chlorides or acid bromides derived from aryl or lower alkanolic acids. Example of anhydrides are anhydrides derived from monocarboxylic acid such as acetic anhydride, benzoic acid anhydride, and lower alkane dicarboxycyclic acid anhydrides, e.g. succinic anhydride as well as chloro formates e.g. trichloro, ethylchloro formate being preferred. A suitable ether protecting group for alcohols are, for example, the tetrahydropyranyl ethers such as 4-methoxy-5,6-dihydroxy-2H-pyranyl ethers. Others are aroylmethylethers such as benzyl, benzhydryl or trityl ethers or  $\alpha$ -lower alkoxy lower alkyl ethers, for example, methoxymethyl or allylic ethers or alkyl silylethers such as trimethylsilylether.

The term "amino protecting group" designates any conventional amino protecting group which can be cleaved to yield the free amino group. The preferred protecting groups are the conventional amino protecting groups utilized in peptide synthesis. Especially preferred are those amino protecting groups which are cleavable under mildly acidic conditions from about pH 2.0 to 3. Particularly preferred amino protecting groups are t-butoxycarbonyl (BOC), carbobenzyloxy (CBZ) and 9-fluorenylmethoxycarbonyl (FMOC).

The term "pharmaceutically acceptable salts" as used herein include any salt with both inorganic or organic pharmaceutically acceptable acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulfonic acid, *para*-toluene sulfonic acid and the like. The term "pharmaceutically acceptable salts" also includes any pharmaceutically acceptable base salt such as amine salts, trialkyl amine salts and the like. Such salts can be formed quite readily by those skilled in the art using standard techniques.

R<sup>3</sup> is cycloalkyl having from 3 to 7 carbon atoms or lower alkyl having from 2 to 4 carbon atoms;

R<sup>4</sup> is -C(O)NHR<sup>40</sup>;

R<sup>40</sup> is hydrogen, lower alkyl, lower alkenyl, hydroxy lower alkyl, halo lower alkyl,  
5 -(CH<sub>2</sub>)<sub>n</sub>-C(O)OR<sup>5</sup> or -C(O)-(CH<sub>2</sub>)<sub>n</sub>-C(O)OR<sup>6</sup>;

R<sup>5</sup> and R<sup>6</sup> are hydrogen or lower alkyl; and

n is 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt thereof.

10       Preferable heteroaromatic residues in R<sup>4</sup> are unsubstituted or mono-substituted five- or six-membered heteroaromatic rings selected from the group consisting of thiazolyl, pyridinyl, imidazolyl, isoxazolyl, oxazolyl, pyridazinyl, pyrimidinyl or thiadiazolyl. Especially preferred are unsubstituted thiazolyl, unsubstituted pyridinyl or pyridinyl substituted by halogen, lower alkyl, hydroxy lower alkyl or -C(O)OR<sup>5</sup>, wherein  
15       R<sup>5</sup> is lower alkyl.

Preferable residues R<sup>40</sup> in accordance with the present invention are lower alkyl or lower alkenyl.

Preferable residues R<sup>1</sup> in accordance with the present invention are hydrogen, halo, nitro and cyano, more preferable are hydrogen or halo.

20       Preferable residues R<sup>2</sup> in accordance with the present invention are hydrogen, lower alkyl sulfonyl, perfluoro-lower alkyl, perfluoro-lower alkyl sulfonyl, halo or -OR<sup>5</sup> wherein R<sup>5</sup> is perfluoro-lower alkyl; more preferable are halo or lower alkyl sulfonyl.

Preferable residues R<sup>3</sup> in accordance with the present invention are cyclopentyl, cyclohexyl or cycloheptyl, more preferable is cyclopentyl.

25

In the compounds described below, unless otherwise indicated, R<sup>4</sup> is a group -C(O)NHR<sup>40</sup>, wherein R<sup>40</sup> is as defined above.

In further amides of the above compound, one of  $R^1$  and  $R^2$  is hydrogen, lower alkyl thio or perfluoro-lower alkyl thio and the other is lower alkyl thio or perfluoro-lower alkyl thio. Examples of such amides are:

- 1-[3-cyclopentyl-2-(4-trifluoromethylsulfanyl-phenyl)-propionyl]-3-methyl urea;  
5 1-[3-cyclopentyl-2-(4-methylsulfanyl-phenyl)-propionyl]-3-methyl urea.

In yet further amides of the above compound, one of  $R^1$  and  $R^2$  is hydrogen or perfluoro-lower alkyl sulfonyl and the other is perfluoro-lower alkyl sulfonyl. Examples of such amides are:

- 1-[3-cyclopentyl-2-(4-trifluoromethanesulfonyl-phenyl)-propionyl]-3-methyl urea;  
10 1-[3-cyclopentyl-2-(3-trifluoromethanesulfonyl-phenyl)-propionyl]-3-methyl urea.

In certain amides of the above compound, at least one of  $R^1$  and  $R^2$  is lower alkyl sulfonyl. Preferably one of  $R^1$  and  $R^2$  is hydrogen or lower alkyl sulfonyl and the other is lower alkyl sulfonyl, and more preferably  $R^2$  is lower alkyl sulfonyl. Examples of such amides are:

- 15 1-[3-cyclopentyl-2-(4-methanesulfonyl-phenyl)-propionyl]-3-methyl urea;  
1-[2-(4-(butane-1-sulfonyl)-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea;  
1-[3-cyclopentyl-2-(4-ethanesulfonyl-phenyl)-propionyl]-3-methyl-urea;  
1-[2-(3,4-bis-methanesulfonyl-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea.

- In other amides of the above compound, at least one of  $R^1$  and  $R^2$  is lower alkyl sulfonyl, one of  $R^1$  and  $R^2$  is cyano or halo and the other, preferably  $R^2$ , is lower alkyl sulfonyl. Examples of such amides are:

- 1-[2-(3-bromo-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea;  
1-[3-cyclopentyl-2-(3-fluoro-4-methanesulfonyl-phenyl)-propionyl]-3-methyl-urea;  
1-[2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea;  
25 1-[2(R)-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea;  
1-[2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionyl]-3-ethyl-urea;  
1-[2-(3-cyano-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea.

In other amides of the above compound, at least one of  $R^1$  and  $R^2$  is lower alkyl sulfonyl, one of  $R^1$  and  $R^2$  is perfluoro-lower alkyl and the other, preferably  $R^2$ , is lower

In certain compounds of this invention,  $R^{40}$  is  $-(CH_2)_n-C(O)OR^5$  or  $-C(O)-(CH_2)_n-C(O)OR^6$ . In some such compounds,  $R^3$  of the amide is cyclopentyl. Preferably  $R^1$  and  $R^2$  are independently halo. Examples of the above amides are:

- 3-{3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido}-propionic acid ethyl ester;  
 5 {3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido}-acetic acid ethyl ester;  
 {3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido}-acetic acid methyl ester;  
 3-{3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido}-propionic acid methyl ester;  
 10 {3-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionyl]-ureido}-acetic acid ethyl ester;  
 3-{3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido}-3-oxo-propionic acid ethyl ester.

In certain compounds of this invention,  $R^{40}$  is hydroxy lower alkyl, or halo lower alkyl. In some such compounds,  $R^3$  of the amide is cyclopentyl. Preferably  $R^1$  and  $R^2$  are  
 15 independently halo, and in addition the amide is in the "R" configuration at the asymmetric carbon shown. Examples of the above amides are:

- 1-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-(2-hydroxy-ethyl)-urea;  
 1-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-(2-hydroxy-propyl)-urea;  
 1-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-(3-hydroxy-propyl)-urea;  
 20 1-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionyl]-3-(2-hydroxy-propyl)-urea;  
 1-(2-chloro-ethyl)-3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-urea;  
 1-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionyl]-3-(3-hydroxy-propyl)-urea.

In the compounds described below, unless otherwise indicated,  $R^4$  is an  
 25 unsubstituted or mono-substituted five- or six-membered heteroaromatic ring connected by a ring carbon atom to the amine group shown, which five- or six-membered heteroaromatic ring contains from 1 to 3 heteroatoms selected from sulfur, oxygen or nitrogen, with one heteroatom being nitrogen which is adjacent to the connecting ring carbon atom; said mono-substituted heteroaromatic ring being monosubstituted at a

- b) one of  $R^1$  and  $R^2$  is lower alkyl sulfonyl, and the other of said  $R^1$  and  $R^2$  is lower alkyl sulfonyl or hydrogen; and
- c) one of  $R^1$  and  $R^2$  is hydrogen and the other of said  $R^1$  and  $R^2$  is lower alkyl or perfluoro-lower alkyl.

5 In accordance with another embodiment of the invention where  $R^3$  is cyclopentyl and  $R^4$  is a mono-substituted thiazole (Compounds I-D2), are those compounds where the mono-substitution is lower alkyl and one of  $R^1$  and  $R^2$  are hydrogen or halogen and the other of  $R^1$  and  $R^2$  is halogen (Compounds I-D2(b)).

Among another embodiment of the compounds I-D are those compounds where  
10 the mono-substituted thiazole is substituted with  $-(CH_2)_n-C(O)OR^7$ , wherein  $n$  is 0 or 1 and  $R^7$  is hydrogen, or lower alkyl (Compounds of I-D2(c)). Among the embodiments of compounds of formula I-D2(c) are those compounds where:

- a) one of  $R^1$  and  $R^2$  is hydrogen and the other of said  $R^1$  and  $R^2$  is halo;
- b)  $R^1$  and  $R^2$  are each independently halo;
- 15 c) one of  $R^1$  or  $R^2$  is nitro, amino or hydrogen and the other of said  $R^1$  and  $R^2$  is nitro or amino; and
- d) one of  $R^1$  and  $R^2$  is lower alkyl sulfonyl, perfluoro-lower alkyl, halogen or hydrogen and the other of said  $R^1$  and  $R^2$  is lower alkyl sulfonyl.

In accordance with another embodiment of this invention, where  $R^3$  and  
20 cyclopentyl and  $R^4$  is a mono-substituted thiazole (Compounds I-D2) are those compounds where the mono-substituted thiazole is substituted with  $-C(O)-C(O)OR^8$ , wherein  $R^8$  is as above (Compounds I-D2(d)). Among the embodiments of compound I-D2(d) are those compounds where:

- a) one of  $R^1$  and  $R^2$  are hydrogen and the other of said  $R^1$  and  $R^2$  is nitro or amino;
- 25 b) one of  $R^1$  and  $R^2$  is halo or perfluoro-lower alkyl and the other of said  $R^1$  and  $R^2$  is perfluoro-lower alkyl, halogen or hydrogen; and
- c) one of  $R^1$  and  $R^2$  is hydrogen or halogen and the other of said  $R^1$  and  $R^2$  is lower alkylsulfonyl.

Other embodiments of the compounds of formula I-D4(b) are those compounds where the pyridine ring is mono-substituted with  $-(CH_2)_n-OR^6$  wherein n and  $R^6$  are as above (Compounds I-D4(b)). Among the embodiments of the compound I-D4(b) are those compounds where:

- 5 a) one of  $R^1$  and  $R^2$  are halo and the other of said  $R^1$  and  $R^2$  is hydrogen or halo; and
- b) one of  $R^1$  and  $R^2$  is lower alkyl sulfonyl or hydrogen and the other of said  $R^1$  and  $R^2$  is lower alkyl sulfonyl.

Another embodiment of compounds where  $R^3$  is cyclopentyl and  $R^4$  is a mono-substituted pyridine ring are those compounds where the pyridine ring is mono-substituted with a halo or perfluoro-lower alkyl substituent, the compound of formula I-D4(c). Among the embodiments of the compound of formula I-D4(c) are those compounds where:

- a) one of  $R^1$  and  $R^2$  is halo or hydrogen and the other is halo; and
- b) one of  $R^1$  and  $R^2$  is halo, nitro or hydrogen and the other is perfluoro-lower alkyl sulfonyl or lower alkyl sulfonyl.

In accordance with another embodiment of this invention are compounds of where  $R^3$  is cyclopentyl and  $R^4$  is a mono-substituted pyridine are those compounds where the pyridine is mono-substituted with a nitro substituent, (Compound I-D4(d)). The embodiments of the compound I-D4(d) include compounds where one of  $R^1$  and  $R^2$  is halo and other of said  $R^1$  or  $R^2$  is hydrogen, halo, or lower alkyl sulfonyl.

In accordance with another embodiment of this invention are compounds of formula I where  $R^3$  is cyclopentyl and  $R^4$  is mono-substituted pyridine and the mono-substitution is a lower alkyl group (Compounds I-D4(e)). Among the embodiments of compounds I-D4(e) are those compounds where one of  $R^1$  and  $R^2$  is halo or hydrogen and the other of  $R^1$  and  $R^2$  is halo, perfluoro-lower alkyl, perfluoro-lower alkyl sulfonyl, or lower alkyl sulfonyl.

In accordance with another embodiment of this invention where  $R^3$  is cyclopentyl and  $R^4$  is a mono-substituted pyridine are those compounds where the mono-substituent is  $-(CH_2)_n-C(O)-NHR^6$ , wherein n and R are as above (Compound I-D4(f)). Among the

Another embodiment of this invention where  $R^3$  is cyclopentyl include compounds where  $R^4$  is unsubstituted pyrimidinyl. The embodiments of those compounds where  $R^3$  is cyclopentyl and  $R^4$  is unsubstituted pyrimidinyl include those compounds where one of  $R^1$  or  $R^2$  is halo, nitro, lower alkyl sulfonyl or perfluoro-lower alkyl and the other is hydrogen or halo.

Another embodiment of this invention includes compounds where  $R^3$  is cyclopentyl where  $R^4$  is an unsubstituted thiadiazolyl ring. Among the embodiments included within those compounds where  $R^3$  is cyclopentyl and  $R^4$  is an unsubstituted thiadiazolyl ring are those compounds wherein one of  $R^1$  or  $R^2$  is halo, nitro, lower alkyl sulfonyl or perfluoro-lower alkyl and the other of said  $R^1$  and  $R^2$  is hydrogen or halo.

In accordance with other embodiments of this invention,  $R^3$  in the compound of formula I can be cycloheptyl or cyclohexyl. The embodiments of the compound of formula I where  $R^3$  is cycloheptyl or cyclohexyl include those compounds where  $R^4$  is thiazolyl which can be mono-substituted or unsubstituted. Embodiments included within such compounds where  $R^3$  is cycloheptyl or cyclohexyl and  $R^4$  is an unsubstituted thiazolyl include those compounds wherein one of  $R^1$  and  $R^2$  is halo, lower alkyl sulfinyl, perfluoro-lower alkyl sulfinyl, perfluoro-lower alkyl or lower alkyl sulfonyl and the other is of said  $R^1$  and  $R^2$  with halo, perfluoro-lower alkyl or hydrogen.

Examples of compounds of formula I according to the present invention, wherein  $R^4$  is a heteroaromatic ring are:

- 2-(3-chloro-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide,
- 2-(4-bromo-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide,
- 2-(4-chloro-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide,
- 3-cyclopentyl-2-(3,4-dichlorophenyl)-N-thiazol-2-yl-propionamide,
- 3-cyclopentyl-N-thiazol-2-yl-2-(4-trifluoromethyl-phenyl)-propionamide,
- 3-cyclopentyl-2-(3-fluoro-4-trifluoromethyl-phenyl)-N-thiazol-2-yl-propionamide,
- 3-cyclopentyl-2-(4-fluoro-3-trifluoromethyl-phenyl)-N-thiazol-2-yl-propionamide,
- 3-cyclopentyl-N-thiazol-2-yl-2-(3-trifluoromethyl-phenyl)-propionamide,

- 3-cyclopentyl-2-(3,4-dihydroxy-phenyl)-N-thiazol-2-yl-propionamide,  
3-cyclopentyl-2-(4-methoxy-phenyl)-N-thiazol-2-yl-propionamide,  
3-cyclopentyl-2-(4-hydroxy-phenyl)-N-thiazol-2-yl-propionamide,  
4-[2-cyclopentyl-1-(thiazol-2-ylcarbamoyl)-ethyl]-benzoic acid methyl ester,  
5 3-cyclopentyl-2-(3-fluoro-4-methoxy-phenyl)-N-thiazol-2-yl-propionamide,  
3-cyclopentyl-2-(3-fluoro-4-hydroxy-phenyl)-N-thiazol-2-yl-propionamide,  
3-cyclopentyl-2-(3,4-dichlorophenyl)-N-(5-hydroxymethyl-thiazol-2-yl)-propionamide,  
3-cyclopentyl-2-(3,4-dichlorophenyl)-N-[4-(2-hydroxyethyl)-thiazol-2-yl]-propionamide,  
2-(4-chloro-phenyl)-3-cyclopentyl-N-(5-hydroxymethyl-thiazol-2-yl)-propionamide,  
10 3-cyclopentyl-2-(3,4-dichlorophenyl)-N-(4-hydroxymethyl-thiazol-2-yl)-propionamide,  
3-cyclopentyl-N-(4-hydroxymethyl-thiazol-2-yl)-2-(4-methanesulfonyl-phenyl)-  
propionamide,  
3-cyclopentyl-N-[4-(2-hydroxyethyl)-thiazol-2-yl]-2-(4-methanesulfonyl-phenyl)-  
propionamide,  
15 3-cyclopentyl-2-(3,4-dichlorophenyl)-N-(4-methyl-thiazol-2-yl)-propionamide,  
3-cyclopentyl-2-(3,4-dichlorophenyl)-N-(5-methyl-thiazol-2-yl)-propionamide,  
{2-[2-(3-chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazol-4-yl}-acetic acid ethyl  
ester,  
{2-[2-(3-chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazol-4-yl}-acetic acid methyl  
20 ester,  
2-[2-(3-chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazole-4-carboxylic acid methyl  
ester,  
2-[2-(3-chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazole-4-carboxylic acid ethyl  
ester,  
25 {2-[2-(4-chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazol-4-yl}-acetic acid ethyl  
ester,  
2-[2-(4-chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazole-4-carboxylic acid methyl  
ester,  
2-[2-(4-chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazole-4-carboxylic acid ethyl  
30 ester,  
{2-[2-(4-chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazol-4-yl}-acetic acid methyl  
ester,  
{2-[3-cyclopentyl-2-(3,4-dichlorophenyl)-propionylamino]-thiazol-4-yl}-acetic acid,  
{2-[3-cyclopentyl-2-(3,4-dichlorophenyl)-propionylamino]-thiazol-4-yl}-acetic acid ethyl  
35 ester,



- {2-[2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionylamino]-thiazol-4-yl}-  
oxo-acetic acid ethyl ester,
- 3-cyclopentyl-2-(3,4-dichlorophenyl)-N-(5-nitro-thiazol-2-yl)-propionamide,  
3-cyclopentyl-2-(3-fluoro-4-trifluoromethyl-phenyl)-N-pyridin-2-yl-propionamide,
- 5 3-cyclopentyl-2-(3,4-dichloro-phenyl)-N-pyridin-2-yl-propionamide,  
3-cyclopentyl-N-pyridin-2-yl-2-(4-trifluoromethyl-phenyl)-2-propionamide,  
3-cyclopentyl-N-thiazol-2-yl-2-(3-trifluoromethyl-phenyl)-propionamide,  
2-(3-chloro-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide,  
2-(4-amino-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide,
- 10 2-(4-cyano-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide,  
2-(4-chloro-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide,  
2-(4-chloro-3-nitro-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide,  
3-cyclopentyl-2-(4-nitro-phenyl)-N-pyridin-2-yl-propionamide,  
2-(4-cyano-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide,
- 15 3-cyclopentyl-2-(4-methylsulfanyl-phenyl)-N-pyridin-2-yl-propionamide,  
3-cyclopentyl-N-pyridin-2-yl-2-(4-trifluoromethylsulfanyl-phenyl)-propionamide,  
3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-N-pyridin-2-yl-propionamide,  
3-cyclopentyl-2-(4-methanesulfonyl-phenyl)-N-pyridin-2-yl-propionamide,  
2-(3-bromo-4-methanesulfonyl-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide,
- 20 2-(3-cyano-4-methanesulfonyl-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide,  
3-cyclopentyl-2-(4-ethanesulfonyl-phenyl)-N-pyridin-2-yl-propionamide,  
2-(3,4-bis-methanesulfonyl-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide,  
2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide,  
3-cyclopentyl-2-(4-methanesulfonyl-3-trifluoromethyl-phenyl)-N-pyridin-2-yl-
- 25 propionamide,  
3-cyclopentyl-N-pyridin-2-yl-2-(4-trifluoromethanesulfonyl-phenyl)-propionamide,  
3-cyclopentyl-2-(3,4-dichloro-phenyl)-N-(5-carboxymethylpyridin)-2-yl-propionamide,  
6-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionylamino]-nicotinic acid methyl ester,  
6-[2-(4-chloro-phenyl)-3-cyclopentyl-propionylamino]-nicotinic acid,
- 30 6-[2-(3-chloro-phenyl)-3-cyclopentyl-propionylamino]-nicotinic acid methyl ester,  
6-[2-(4-chloro-phenyl)-3-cyclopentyl-propionylamino]-nicotinic acid methyl ester,  
6-[3-cyclopentyl-2-(4-nitro-phenyl)-propionylamino]-nicotinic acid methyl ester,  
6-[2-(4-amino-phenyl)-3-cyclopentyl-propionylamino]-nicotinic acid methyl ester,

- 3-cyclopentyl-N-(5-methyl-pyridin-2-yl)-2-(4-trifluoromethanesulfonyl-phenyl)-propionamide,  
 3-cyclopentyl-2-(4-fluoro-3-trifluoromethyl-phenyl)-N-(5-methyl-pyridin-2-yl)-propionamide,  
 5 6-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionylamino]-N-methyl-nicotinamide,  
 3-cyclopentyl-2-(3,4-dichlorophenyl)-N-(1H-imidazol-2-yl)-propionamide,  
 3-cyclopentyl-2-(3,4-dichlorophenyl)-N-(5-methyl-isoxazol-3-yl)-propionamide,  
 3-cyclopentyl-2-(3,4-dichlorophenyl)-N-oxazol-2-yl-propionamide,  
 3-cyclopentyl-2-(3,4-dichlorophenyl)-N-pyridazin-3-yl-propionamide,  
 10 3-cyclopentyl-2-(3,4-dichlorophenyl)-N-pyrimidin-2-yl-propionamide,  
 3-cyclopentyl-2-(3,4-dichlorophenyl)-N-pyrimidin-6-yl-propionamide,  
 3-cyclopentyl-2-(4-nitro-phenyl)-N-pyrimidin-4-yl-propionamide,  
 3-cyclopentyl-2-(3,4-dichlorophenyl)-N-[1,3,4]thiadiazol-2-yl-propionamide,  
 2-[4-methanesulfonyl phenyl]-3-cyclohexyl N-thiazol-2-yl-propionamide, and  
 15 2-[4-methanesulfonyl phenyl]-3-cycloheptyl N-thiazol-2-yl-propionamide.

Examples of compounds of formula I according to the present invention, wherein  $R^4$  is a residue  $-C(O)NHR^{40}$  and  $R^{40}$  is as defined above, are:

- 1-(3-cyclopentyl-2-phenyl-propionyl)-3-methyl-urea,  
 20 1-[2-(3-chloro-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea,  
 1-[2-(4-chloro-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea,  
 1-[2-(4-cyano-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea,  
 1-[2-(4-bromo-phenyl)-3-cyclopentyl-propionyl]-3-methyl urea,  
 [3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-urea,  
 25 1-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-methyl-urea,  
 1-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionyl]-3-ethyl-urea,  
 1-allyl-3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-urea,  
 1-allyl-3-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionyl]-urea,  
 1-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-ethyl-urea,  
 30 1-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionyl]-3-methyl-urea,  
 1-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-isopropyl-urea,  
 1-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-propyl-urea,

- {3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido}-acetic acid ethyl ester,  
{3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido}-acetic acid methyl ester,  
3-{3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido}-propionic acid methyl ester,  
5 {3-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionyl]-ureido}-acetic acid ethyl ester,  
3-{3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido}-3-oxo-propionic acid ethyl ester,  
1-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-(2-hydroxy-ethyl)-urea,  
1-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-(2-hydroxy-propyl)-urea,  
10 1-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-(3-hydroxy-propyl)-urea,  
1-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionyl]-3-(2-hydroxy-propyl)-urea,  
1-(2-chloro-ethyl)-3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-urea, and  
1-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionyl]-3-(3-hydroxy-propyl)-urea.

- 15 It will be appreciated that the compounds of formula I may be derivatised at functional groups to provide derivatives which are capable of conversion back to the parent compounds in vivo. Additionally, any physiologically acceptable equivalents of the compounds of formula I, which are capable of producing the parent compounds of formula I in vivo, are within the scope of this invention.

20

The compound of formula I can be prepared starting from the compound of formula V by the following Reaction Scheme:

which is adjacent to the connecting ring carbon atom; said mono-substituted heteroaromatic ring being monosubstituted at a position on a ring carbon atom other than adjacent to said connecting carbon atom with a substituent selected from the group consisting of lower alkyl, halo, nitro, cyano,  $-(CH_2)_n-OR^6$ ,  $-(CH_2)_n-C(O)OR^7$ ,  $-(CH_2)_n-C(O)NHR^6$ ,  $-C(O)-C(O)OR^8$  or  $-(CH_2)_n-NHR^6$ , wherein  $R^6$ ,  $R^7$ ,  $R^8$  and  $n$  are as defined above;  $R^{15}$  is hydrogen or lower alkyl; and  $R^{41}$  is lower alkyl, lower alkenyl, hydroxy lower alkyl, halo lower alkyl or  $-(CH_2)_n-C(O)OR^5$ , wherein  $R^5$  is hydrogen or lower alkyl and  $n$  is as defined above.

The carboxylic acids and their lower alkyl esters of formula V wherein one of  $R^1$  and  $R^2$  is nitro, cyano, thio, amino, chloro, bromo, or iodo and the other is hydrogen are commercially available. In cases, where only the carboxylic acids are available, they can be converted to the corresponding esters of lower alkyl alcohols using any conventional esterification methods. All the reactions hereto forward are to be carried out on lower alkyl esters of the carboxylic acids of formula V. The amino substituted compounds of formula V can be converted to other substituents either before or after conversion to the compounds of formulae I-a, I-b, I-c or I-d. In this respect, the amino groups can be diazotized to yield the corresponding diazonium compound, which *in situ* can be reacted with the desired lower alkyl thiol, perfluoro-lower alkyl thiol (see for example, Baleja, J.D. *Synth. Comm.* 1984, 14, 215; Giam, C. S.; Kikukawa, K., *J. Chem. Soc. Chem. Comm.* 1980, 756; Kau, D.; Krushniski, J. H.; Robertson, D. W., *J. Labelled Compd Rad.* 1985, 22, 1045; Oade, S.; Shinham, K.; Kim, Y. H., *Bull Chem Soc. Jpn.* 1980, 53, 2023; Baker, B. R.; et al, *J. Org. Chem.* 1952, 17, 164), or alkaline earth metal cyanide, to yield corresponding compounds of formula V, where one of the substituents is lower alkyl thio, perfluoro-lower alkyl thio, or cyano, and the other is hydrogen. If desired, the lower alkyl thio or perfluoro-lower alkyl thio compounds can then be converted to the corresponding lower alkyl sulfonyl or perfluoro-lower alkyl sulfonyl substituted compounds of formula V by oxidation. Any conventional method of oxidizing alkyl thio substituents to sulfones can be utilized to effect this conversion.

If it is desired to produce compounds of formula V wherein one of  $R^1$  and  $R^2$  is a lower alkyl or perfluoro-lower alkyl group, the corresponding halo substituted compounds

corresponding compound of formula V where both  $R^1$  and  $R^2$  are iodine or bromine via a diazotization reaction. Any conventional method of converting amino group to an iodo or bromo group (see for example, Lucas, H. J.; Kennedy, E. R. *Org. Synth. Coll. Vol. II* 1943, 351) can be utilized to effect this conversion. If it is desired to produce compounds of formula V, where both  $R^1$  and  $R^2$  are lower alkyl thio or perfluoro-lower alkyl thio groups, the compound of formula V where  $R^1$  and  $R^2$  are amino can be used as starting material. Any conventional method of converting aryl amino group to aryl thioalkyl group can be utilized to effect this conversion. If it is desired to produce compounds of formula V where  $R^1$  and  $R^2$  are lower alkyl sulfonyl or lower perfluoro alkyl sulfonyl, the corresponding compounds of formula V where  $R^1$  and  $R^2$  are lower alkyl thio or perfluoro-lower alkyl thio can be used as starting material. Any conventional method of oxidizing alkyl thio substituents to sulfones can be utilized to effect this conversion.

If it is desired to produce compounds of formula V, where both  $R^1$  and  $R^2$  are substituted with lower alkyl or perfluoro-lower alkyl groups, the corresponding halo substituted compounds of formula V can be used as starting materials. Any conventional method of converting an aromatic halo group to the corresponding alkyl or perfluoro-lower alkyl group can be utilized to effect this conversion.

If it is desired to produce compounds of formula V, where one or both of  $R^1$  and  $R^2$  are substituted with sulfonamido, the corresponding compounds where one or both of  $R^1$  and  $R^2$  are substituted with nitro can be used as starting materials. Any standard method of converting a nitrophenyl compound to the corresponding sulfonamidophenyl compound can be used to effect this conversion.

The carboxylic acids corresponding to the compounds of formula V where one of  $R^1$  and  $R^2$  is nitro and the other is halo are known from the literature (see for 4-chloro-3-nitrophenyl acetic acid, Tadayuki, S.; Hiroki, M.; Shinji, U.; Mitsuhiro, S. Japanese patent, JP 71-99504, *Chemical Abstracts* 80:59716; see for 4-nitro-3-chlorophenyl acetic acid, Zhu, J.; Beugelmans, R.; Bourdet, S.; Chastanet, J.; Rousssi, G. *J. Org. Chem.* **1995**, *60*, 6389; Beugelmans, R.; Bourdet, S.; Zhu, J. *Tetrahedron Lett.* **1995**, *36*, 1279). These carboxylic acids can be converted to the corresponding lower alkyl esters using any

aromatic thio ether group to the corresponding sulfone group can be utilized to effect this conversion.

If it is desired to produce compounds of formula V where one of  $R^1$  and  $R^2$  is halo and the other is lower alkyl thio or perfluoro-lower alkyl thio, the corresponding  
5 compounds where one of  $R^1$  and  $R^2$  is amino and the other is lower alkyl thio or perfluoro-lower alkyl thio can be used as starting materials. Any conventional method of diazotizing an aromatic amino group and conversion of it *in situ* to an aromatic halide can be utilized to effect this conversion.

If it is desired to produce compounds of formula V where one of  $R^1$  and  $R^2$  is halo  
10 and the other is lower alkyl sulfonyl or perfluoro-lower alkyl sulfonyl, the corresponding compounds where one of  $R^1$  and  $R^2$  is halo and the other is lower alkyl thio or perfluoro-lower alkyl thio can be used as starting materials. Any conventional method of oxidizing an aromatic thio ether to the corresponding sulfone can be utilized to effect this conversion. If it is desired to produce compounds of various combinations of lower alkyl  
15 and perfluoro-lower alkyl groups of compounds of formula V, the corresponding halo substituted compounds of formula V can be used as starting materials. Any conventional method of converting an aromatic halo group to the corresponding alkyl group can be utilized to effect this conversion.

If one wishes to prepare the compound formula V where one of  $R^1$  and  $R^2$  is nitro  
20 and the other is amino, the compound of formula V where one of  $R^1$  and  $R^2$  is nitro and other is chloro can be used as a starting material. The chloro substituent on the phenyl ring can be converted to an iodo substituent (see for example, Bunnett, J. F.; Conner, R. M.; *Org. Synth. Coll Vol V*, 1973, 478; Clark, J. H.; Jones, C. W. *J. Chem. Soc. Chem. Commun.* 1987, 1409), which in turn can be reacted with an azide transferring agent to  
25 form the corresponding azide (see for example, Suzuki, H.; Miyoshi, K.; Shinoda, M. *Bull. Chem. Soc. Jpn*, 1980, 53, 1765). This azide can then be reduced in a conventional manner to form the amine substituent by reducing it with commonly used reducing agent for converting azides to amines (see for example, Soai, K.; Yokoyama, S.; Ookawa, A. *Synthesis*, 1987, 48).

all of the reactions described to produce various substituents of  $R^1$  and  $R^2$  in the compound of formula I can also be carried out on the compounds of formulae I-a, I-b I-c or I-d.

5        In the first step of this Reaction Scheme, the alkyl halide of formula VI is reacted with the compound of formula V, to produce the compound of formula VII. In this reaction, if in the compounds of formula V,  $R^1$  or  $R^2$  is an amino group, such amino group(s) have to be protected before carrying out the alkylation reaction with the alkyl halide of formula VI. The amino group can be protected with any conventional acid removable group (for example, for t-butyloxycarbonyl group see, Bodanszky, M. 10 *Principles of Peptide Chemistry, Springer -Verlag, New York, 1984*, p 99). The protecting group has to be removed from the amino groups after preparing the corresponding amine protected compounds of formulae I-a, I-b, I-c or I-d to obtain the corresponding amines. The compound of formula V is an organic acid having an alpha 15 carbon atom and the compound of formula VI is an alkyl halide so that alkylation occurs at the alpha carbon atom of this carboxylic acid. This reaction is carried out by any conventional means of alkylation of the alpha carbon atom of a lower alkyl ester of a carboxylic acid. Generally, in these alkylation reactions any alkyl halide is reacted with the anion generated from any acetic acid ester. The anion can be generated by using a 20 strong organic base such as lithium diisopropylamide, *n*-butyl lithium as well as other organic lithium bases. In carrying out this reaction, low boiling ether solvents are utilized such as tetrahydrofuran at low temperatures from -80°C to about -10°C being preferred. However, any temperature from -80°C to room temperature can be used.

25        The compound of formula VII can be converted to the compound of formula XII by any conventional procedure to convert a carboxylic acid ester to an acid. The compound of formula XII can then be condensed with the compound of formula VIII via conventional peptide coupling to produce the compound of formula I-d. In carrying out this reaction, any conventional method of condensing a primary amine with a carboxylic acid can be utilized to effect this conversion. The required amino heteroaromatic

When  $R^{41}$  is a lower alkenyl group in the compound of formula I-a, this compound can be converted to the corresponding hydroxy lower alkyl group by conventional hydroboration at the olefinic group to produce a corresponding hydroxy group. The hydroxy group, if desired, can be converted to a halo group. Any method of halogenating a hydroxy group can be used in accordance with this invention.

On the other hand, if it is desired to produce the compound of formula I-b the compound of formula XII is first converted to the methyl ester of formula XI, and thereafter reacted with urea to produce the compound of formula I-b. This reaction is carried out by utilizing any conventional means of reacting a methyl ester with urea to form the corresponding condensation product.

The compound of formula I-c, i.e. the compound of formula I wherein  $R^4$  is  $-C(O)NHR^{40}$  and  $R^{40}$  is  $-CO-(CH_2)_n-C(O)OR^6$ , is produced from the monoacid chloride XIII of the monoester of the corresponding dicarboxylic acid. The monoacid chloride XIII is coupled with the compounds of formula I-b using standard coupling methods.

The compound of formula VII has an asymmetric carbon atom through which the group  $-CH_2R^3$  and the acid amide substituents are connected. In accordance with this invention, the preferred stereoconfiguration of this group is R.

If it is desired to produce the R or the S isomer of the compound of formula I, this compound can be separated into these isomers by any conventional chemical means. Among the preferred chemical means is to react the compound of formula XII with an optically active base. Any conventional optically active base can be utilized to carry out this resolution. Among the preferred optically active bases are the optically active amine bases such as alpha-methylbenzylamine, quinine, dehydroabietylamine and alpha-methylnaphthylamine. Any of the conventional techniques utilized in resolving organic acids with optically active organic amine bases can be utilized in carrying out this reaction.

In the resolution step, the compound of formula XII is reacted with the optically active base in an inert organic solvent medium to produce salts of the optically active amine with both the R and S isomers of the compound of formula XII. In the formation



The following compounds were tested and found to have excellent glucokinase activator *in vivo* activity when administered orally in accordance with the assay described in Example B:

- 3-Cyclopentyl-2-(4-methanesulfonyl-phenyl)-N-thiazol-2-yl-propionamide;
- 5 3-Cyclopentyl-N-thiazol-2-yl-2-(4-trifluoromethoxy-phenyl)-propionamide;
- 3-Cyclopentyl-N-thiazol-2-yl-2-(4-trifluoromethanesulfonyl-phenyl)-propionamide;
- 3-Cyclopentyl-2(R)-(3,4-dichloro-phenyl)-N-pyridin-2-yl-propionamide;
- 6-[3-Cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionylamino]-nicotinic acid methyl ester;
- 10 N-(5-Chloro-pyridin-2-yl)-3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionamide;
- 3-Cyclopentyl-N-pyridin-2-yl-2-(4-trifluoromethanesulfonyl-phenyl)-propionamide;
- 3-Cyclopentyl-N-(5-methyl-pyridin-2-yl)-2-(4-trifluoromethanesulfonyl-phenyl)-propionamide;
- 15 3-Cyclopentyl-2(R)-(3,4-dichloro-phenyl)-N-(5-hydroxymethyl-pyridin-2-yl) propionamide;
- 6-[3-Cyclopentyl-2-(4-trifluoromethanesulfonyl-phenyl)-propionylamino]-nicotinic acid methyl ester;
- 3-Cyclopentyl-2-(3-fluoro-4-trifluoromethyl-phenyl)-N-pyridin-2-yl-propionamide;
- 3-Cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-N-pyridin-2-yl-propionamide;
- 20 2-(3-Bromo-4-methanesulfonyl-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide;
- 2-(3-Cyano-4-methanesulfonyl-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide;
- 2-(4-Chloro-3-nitro-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide;
- 2-(3-Chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide;
- 25 N-(5-Bromo-pyridin-2-yl)-2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionamide;
- 2-[3-Chloro-4-methanesulfonyl-phenyl]-3-cyclopentyl-N-thiazol-2-yl-propionamide;
- (2R)-3-Cyclopentyl-2-(4-methanesulfonylphenyl)-N-thiazol-2-yl-propionamide;
- 2-(3-Bromo-4-methanesulfonyl-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide;
- 2-(3-Cyano-4-methanesulfonyl-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide;
- 30 3-Cyclopentyl-2-(4-ethanesulfonyl-phenyl)-N-thiazol-2-yl-propionamide;
- 3-Cyclopentyl-2-(4-methanesulfonyl-3-trifluoromethyl-phenyl)-N-thiazol-2-yl-propionamide; and
- N-(5-Bromo-pyridin-2-yl)-2(R)-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionamide.

acid or salts thereof. Suitable excipients for use with soft gelatine capsules include for example vegetable oils, waxes, fats, semi-solid or liquid polyols etc.; according to the nature of the active ingredients it may however be the case that no excipient is needed at all for soft gelatine capsules. For the preparation of solutions and syrups, excipients  
5 which may be used include for example water, polyols, saccharose, invert sugar and glucose. For injectable solutions, excipients which may be used include for example water, alcohols, polyols, glycerine, and vegetable oils. For suppositories, and local or percutaneous application, excipients which may be used include for example natural or hardened oils, waxes, fats and semi-solid or liquid polyols.

10

The pharmaceutical compositions may also contain preserving agents, solubilising agents, stabilising agents, wetting agents, emulsifiers, sweeteners, colorants, odorants, salts for the variation of osmotic pressure, buffers, coating agents or antioxidants. As mentioned earlier, they may also contain other therapeutically valuable agents. It is a  
15 prerequisite that all adjuvants used in the manufacture of the preparations are non-toxic.

Preferred forms of use are intravenous, intramuscular or oral administration, most preferred is oral administration. The dosages in which the compounds of formula (I) are administered in effective amounts depend on the nature of the specific active ingredient,  
20 the age and the requirements of the patient and the mode of application. In general, dosages of about 1-100 mg/kg body weight per day come into consideration.

This invention will be better understood from the following examples, which are for purpose of illustration and are not intended to limit the invention defined in the claims  
25 that follow thereafter.

thiazol-5-yl}-oxo-acetic acid ethyl ester as a white solid: mp 129-131°C; FAB-HRMS m/e calcd for  $C_{21}H_{22}Cl_2N_2O_4S$  (M+H)<sup>+</sup> 469.0755, found 469.0765.

- (c) From 3-cyclopentyl-2-(3,4-dichlorophenyl)-propionic acid and (2-amino-thiazol-4-yl)-acetic acid ethyl ester: {2-[3-Cyclopentyl-2-(3,4-dichlorophenyl)-propionylamino]-thiazol-4-yl}-acetic acid ethyl ester as a yellow solid: mp 138-139°C; FAB-HRMS m/e calcd for  $C_{21}H_{24}Cl_2N_2O_3S$  (M+H)<sup>+</sup> 455.0963, found 455.0960.

- (d) From 3-cyclopentyl-2-(3,4-dichlorophenyl)-propionic acid and 2-amino-5-methylthiazole: 3-Cyclopentyl-2-(3,4-dichlorophenyl)-N-(5-methyl-thiazol-2-yl)-propionamide as a white solid: mp 142-143°C; EI-HRMS m/e calcd for  $C_{18}H_{20}Cl_2N_2OS$  (M<sup>+</sup>) 382.0673, found 382.0679.

(e) From 3-cyclopentyl-2-(3,4-dichlorophenyl)-propionic acid and 2-amino-4-methylthiazole: 3-Cyclopentyl-2-(3,4-dichlorophenyl)-N-(4-methyl-thiazol-2-yl)-propionamide as a white foam: mp 151-152°C; FAB-HRMS m/e calcd for  $C_{18}H_{20}Cl_2N_2OS$  (M+H)<sup>+</sup> 383.0751, found 383.0758.

- (f) From 3-cyclopentyl-2-(3,4-dichlorophenyl)-propionic acid and 2-amino-thiazole-4-carboxylic acid ethyl ester: 2-[3-Cyclopentyl-2-(3,4-dichlorophenyl)-propionylamino]-thiazole-4-carboxylic acid ethyl ester as a white solid: mp 104-107°C; FAB-HRMS m/e calcd for  $C_{20}H_{22}Cl_2N_2O_3S$  (M+H)<sup>+</sup> 441.0807, found 441.0808.

- (g) From 3-cyclopentyl-2-(3,4-dichlorophenyl)-propionic acid and 2-amino-thiazole-5-carboxylic acid ethyl ester: 2-[3-Cyclopentyl-2-(3,4-dichlorophenyl)-propionylamino]-thiazole-5-carboxylic acid ethyl ester as a light yellow solid: mp 136-137°C; FAB-HRMS m/e calcd for  $C_{20}H_{22}Cl_2N_2O_3S$  (M+H)<sup>+</sup> 441.0807, found 441.0803.

- (h) From 3-cyclopentyl-2-(3,4-dichlorophenyl)-propionic acid and 2-amino-5-nitrothiazole: 3-Cyclopentyl-2-(3,4-dichlorophenyl)-N-(5-nitro-thiazol-2-yl)-propionamide as an orange solid: mp 67-71°C; FAB-HRMS m/e calcd for  $C_{17}H_{17}Cl_2N_3O_3S$  (M+H)<sup>+</sup> 414.0446, found 414.0442.

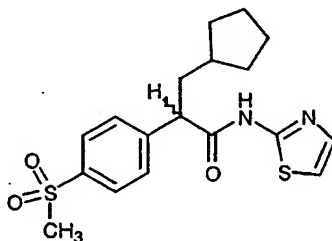
(i) From 3-cyclopentyl-2-(3,4-dichlorophenyl)-propionic acid and 2-amino-thiazole-4-carboxylic acid amide: 2-[3-Cyclopentyl-2-(3,4-dichlorophenyl)-propionylamino]-

A solution of 2-(4-bromo-phenyl)-3-cyclopentyl-propionic acid (1.01 g, 3.39 mmol) in methylene chloride (8.5 mL) was treated with 2 drops of dry *N,N*-dimethylformamide. The reaction mixture was cooled to 0°C and then treated with oxalyl chloride (3 mL, 33.98 mmol). The reaction mixture was stirred at 0°C for 10 min and then stirred at 25°C  
5 for 15 h. The reaction mixture was concentrated *in vacuo*. The resulting yellow oil was dissolved in a small amount of methylene chloride and slowly added to a cooled solution (0°C) of 2-aminothiazole (680.6 mg, 6.79 mmol) and *N,N*-diisopropylethylamine (1.2 mL, 6.79 mmol) in methylene chloride (17 mL). The resulting reaction mixture was stirred at 0°C for 10 min and then at 25°C for 15 h. The reaction mixture was  
10 concentrated *in vacuo* to remove methylene chloride. The resulting residue was diluted with ethyl acetate (200 mL). The organic phase was washed with a 10% aqueous hydrochloric acid solution (2 x 100 mL), washed with a saturated aqueous sodium bicarbonate solution (2 x 100 mL), and washed with a saturated aqueous sodium chloride solution (1 x 100 mL). The organic layer was then dried over sodium sulfate, filtered, and  
15 concentrated *in vacuo* to afford 2-(4-bromo-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide (1.23 g, 95%) as an orange solid which was used in subsequent reactions without further purification. An analytical sample was recrystallized from ethyl acetate to provide a cream solid: mp 201-202°C; EI-HRMS *m/e* calcd for C<sub>17</sub>H<sub>19</sub>BrN<sub>2</sub>OS (M<sup>+</sup>) 378.0401, found 378.0405.

20

### Example 3

#### (A) 3-Cyclopentyl-2-(4-methanesulfonyl-phenyl)-N-thiazol-2-yl-propionamide



allowed to warm to 25°C over 30 min. The brown reaction mixture was then treated with 2-aminothiazole (4.98 g, 49.69 mmol). The resulting reaction mixture was stirred at 25°C for 19 h. The reaction mixture was then concentrated *in vacuo* to remove methylene chloride. The remaining black residue was diluted with a 10% aqueous hydrochloric acid solution (400 mL) and then extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (1 x 200 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/1 hexanes/ethyl acetate then 1/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-methanesulfonyl-phenyl)-N-thiazol-2-yl-propionamide (4.49 g, 72%) as a white solid: mp 216-217°C; EI-HRMS m/e calcd for C<sub>18</sub>H<sub>22</sub>N<sub>2</sub>O<sub>5</sub>S<sub>2</sub> (M<sup>+</sup>) 378.1072, found 378.1071.

(B) In an analogous manner, there were obtained:

(a) From 3-cyclopentyl-2-(4-methanesulfonyl-phenyl)propionic acid and 2-aminothiazole-4-carboxylic acid methyl ester: 2-[3-Cyclopentyl-2-(4-methanesulfonyl-phenyl)-propionylamino]-thiazole-4-carboxylic acid methyl ester as a tan solid: mp 126-128°C; EI-HRMS m/e calcd for C<sub>20</sub>H<sub>24</sub>N<sub>2</sub>O<sub>5</sub>S<sub>2</sub> (M<sup>+</sup>) 436.1127, found 436.1119.

(b) From 3-cyclopentyl-2-(4-methanesulfonyl-phenyl)propionic acid and 2-aminothiazole-4-carboxylic acid ethyl ester: 2-[3-Cyclopentyl-2-(4-methanesulfonyl-phenyl)-propionylamino]-thiazole-4-carboxylic acid ethyl ester as a light yellow solid: mp 101-103°C; EI-HRMS m/e calcd for C<sub>21</sub>H<sub>26</sub>N<sub>2</sub>O<sub>5</sub>S<sub>2</sub> (M<sup>+</sup>) 450.1283, found 450.1284.

(c) From 3-cyclopentyl-2-(4-methanesulfonyl-phenyl)propionic acid and methyl 2-amino-4-thiazoleacetate: {2-[3-Cyclopentyl-2-(4-methanesulfonyl-phenyl)-propionylamino]-thiazol-4-yl}-acetic acid methyl ester as a yellow solid: mp 63-65°C; EI-HRMS m/e calcd for C<sub>21</sub>H<sub>26</sub>N<sub>2</sub>O<sub>5</sub>S<sub>2</sub> (M<sup>+</sup>) 450.1283, found 450.1294.

(d) From 3-cyclopentyl-2-(4-methanesulfonyl-phenyl)propionic acid and ethyl 2-amino-4-thiazoleacetate: {2-[3-Cyclopentyl-2-(4-methanesulfonyl-phenyl)-propionylamino]-

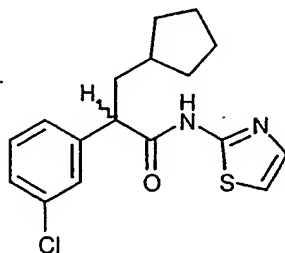
h. The reaction was then concentrated *in vacuo*. The residue was dissolved in methylene chloride (50 mL) and washed with a saturated aqueous sodium bicarbonate solution (2 x 25 mL), water (1 x 50 mL), and a saturated aqueous sodium chloride solution (1 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to give (4-nitro-phenyl)-acetic acid methyl ester (5.27 g, 97.9%) as a pale yellow solid: mp 29-30°C; EI-HRMS m/e calcd for C<sub>9</sub>H<sub>9</sub>NO<sub>4</sub> (M<sup>+</sup>) 195.0531, found 195.0532.

A solution of freshly prepared lithium diisopropylamide (43.3 mL of a 0.3M stock solution, 12.99 mmol) cooled to -78°C was treated with (3-nitro-phenyl)-acetic acid methyl ester (2.45 g, 12.56 mmol) in tetrahydrofuran/1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (32 mL, 3:1). The resulting solution was stirred at -78°C for 45 min. Iodomethylcyclopentane (2.78 g, 13.23 mmol) was then added in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (2.78 mL), and the mixture was stirred at -78°C for 3 h. The reaction was warmed to 25°C and was stirred at 25°C for 16 h. The reaction mixture was then quenched by the dropwise addition of a saturated aqueous ammonium chloride solution (25 mL) and was concentrated *in vacuo*. The residue was diluted with water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The organics were washed with a saturated aqueous lithium chloride solution (2 x 25 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh 80/20 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(3-nitro-phenyl)-propionic acid methyl ester (1.63 g, 46.8%) as pale yellow oil: EI-HRMS m/e calcd for C<sub>15</sub>H<sub>19</sub>NO<sub>4</sub> (M<sup>+</sup>) 277.1314, found 277.1317.

A solution of 3-cyclopentyl-2-(3-nitro-phenyl)-propionic acid methyl ester (0.55 g, 2.0 mmol) in tetrahydrofuran/water (10 mL, 3:1) was treated with lithium hydroxide (185 mg, 4.40 mmol). The reaction was stirred at 25°C for 48 h. The tetrahydrofuran was then removed *in vacuo*. The residue was diluted with water (25 mL) and extracted with ether (1 x 20 mL). The aqueous layer was acidified to pH = 2 with a 3N aqueous hydrochloric

## Example 6

## 2-(3-Chloro-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide



(3-Chloro-phenyl)-acetic acid (6.03 g, 0.03 mol) was dissolved in ethanol (37.7 mL) and  
5 treated with a catalytic amount of sulfuric acid. The reaction mixture was refluxed for  
12 h. The reaction was concentrated *in vacuo*. Flash chromatography (Merck Silica gel  
60, 230-400 mesh, 50/50 hexanes/ethyl acetate) afforded (3-chloro-phenyl)-acetic acid  
ethyl ester (6.10 g, 86.8%) as a clear oil: EI-HRMS *m/e* calcd for  $C_{10}H_{11}ClO_2$  ( $M^+$ )  
198.0448, found 198.0442.

10

A solution of freshly prepared lithium diisopropylamide (23 mL of 0.31M stock solution,  
7.13 mmol) cooled to  $-78^{\circ}C$  was treated with (3-chloro-phenyl)-acetic acid ethyl ester  
(1.28 g, 6.48 mmol) in tetrahydrofuran/hexamethylphosphoramide (16.1 mL, 3:1). The  
resulting solution was stirred at  $-78^{\circ}C$  for 45 min. At this time, the reaction was treated  
15 with a solution of iodomethylcyclopentane (1.50 g, 7.13 mmol) in  
hexamethylphosphoramide (1 mL). The reaction mixture was stirred at  $-78^{\circ}C$  for 4 h.  
The reaction was warmed to  $25^{\circ}C$  and stirred at  $25^{\circ}C$  for 16 h. The reaction mixture was  
then quenched by the dropwise addition of a saturated aqueous ammonium chloride  
solution (20 mL). This mixture was poured into water (100 mL) and extracted with ethyl  
20 acetate (3 x 50 mL). The organics were dried over sodium sulfate, filtered, and  
concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 75/25  
hexanes/ethyl acetate) afforded 2-(3-chloro-phenyl)-3-cyclopentyl-propionic acid ethyl  
ester (1.70 g, 93%) as a yellow oil: EI-HRMS *m/e* calcd for  $C_{16}H_{21}ClO_2$  ( $M^+$ ) 280.1230,  
found 280.1238.

60, 230-400 mesh, 50/50 hexanes/ethyl acetate) afforded (4-chloro-phenyl)-acetic acid ethyl ester (6.45 g, 88%) as a pale yellow solid: mp 39-41°C; EI-HRMS m/e calcd for  $C_{10}H_{11}ClO_2$  ( $M^+$ ) 198.0448, found 198.0452.

- 5 A solution of freshly prepared lithium diisopropylamide (23.0 mL of 0.31M stock solution, 7.13 mmol) cooled to -78°C was treated with (4-chloro-phenyl)-acetic acid ethyl ester (1.28 g, 6.48 mmol) in tetrahydrofuran/hexamethylphosphoramide (16.1 mL, 3:1). The resulting solution was stirred at -78°C for 45 min. At this time, the reaction was treated with a solution of iodomethylcyclopentane (1.50 mg, 7.13 mmol) in
- 10 hexamethylphosphoramide (1 mL). The reaction mixture was stirred at -78°C for 4 h. The reaction was warmed to 25°C and stirred at 25°C for 16 h. The reaction mixture was then quenched by the dropwise addition of a saturated aqueous ammonium chloride solution (20 mL). This mixture was poured into water (100 mL) and extracted with ethyl acetate (3 x 50 mL). The organics were dried over sodium sulfate, filtered, and
- 15 concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 75/25 hexanes/ethyl acetate) afforded 2-(4-chloro-phenyl)-3-cyclopentyl-propionic acid ethyl ester (1.65 g, 90.9%) as a yellow oil: EI-HRMS m/e calcd for  $C_{16}H_{21}Cl_2O_2$  ( $M^+$ ) 280.1230, found 280.1227.
- 20 A mixture of 2-(4-chloro-phenyl)-3-cyclopentyl-propionic acid ethyl ester (1.65 g, 5.89 mmol) and methyl urea (654 mg, 8.83 mmol) in a solution of magnesium methoxide in methanol (7.4 wt%, 16.9 mL, 11.78 mmol) was refluxed at 100°C for 6 h. The reaction mixture was then concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 75/25 hexanes/ethyl acetate) afforded 1-[2-(4-chloro-phenyl)-3-
- 25 cyclopentyl-propionyl]-3-methyl-urea (105.3 mg, 5.8 %) as a white solid: mp 145-147°C; EI-HRMS m/e calcd for  $C_{16}H_{21}ClN_2O_2$  ( $M^+$ ) 308.1292, found 308.1291. The methyl ester of the starting material was recovered from the reaction mixture due to transesterification.



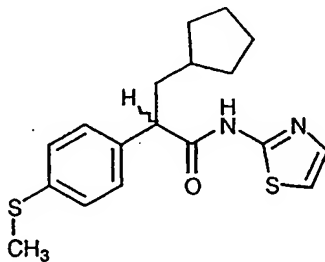
(634.9 mg, 65%) as a white solid: mp 94-95°C; EI-HRMS  $m/e$  calcd for  $C_{15}H_{17}F_3O_2$  ( $M^+$ ) 309.1079, found 309.1072.

A solution of 3-cyclopentyl-2-(4-trifluoromethyl-phenyl)-propionic acid (185 mg, 0.64 mmol) in methylene chloride (6.5 mL) was cooled to 0°C and was treated with a 2.0M solution of oxalyl chloride in methylene chloride (0.35 mL, 0.71 mmol) and a few drops of *N,N*-dimethylformamide. The reaction mixture was stirred at 0°C for 10 min and at 25°C for 30 min. The reaction mixture was then treated with a solution of 2-aminothiazole (142 mg, 1.42 mmol) in tetrahydrofuran (3.23 mL) and *N,N*-diisopropylethylamine (0.27 mL, 1.55 mmol). The solution was stirred at 25°C for 5 h. At this time, the reaction was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 80/20 hexanes/ethyl acetate) afforded 3-cyclopentyl-*N*-thiazol-2-yl-2-(4-trifluoromethyl-phenyl)-propionamide (127 mg, 53.3%) as a white solid: mp 210-212°C; EI-HRMS  $m/e$  calcd for  $C_{18}H_{19}F_3N_2OS$  ( $M^+$ ) 368.1175, found 368.1170.

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### Example 9

#### 3-Cyclopentyl-2-(4-methylsulfanyl-phenyl)-*N*-thiazol-2-yl-propionamide



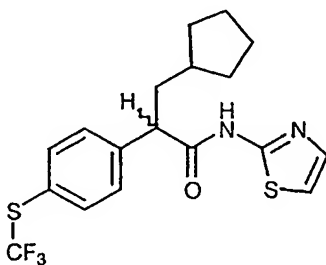
A solution of diisopropylamine (3.2 mL, 23.16 mmol) in dry tetrahydrofuran (10.3 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (3.4 mL) was cooled to -78°C under nitrogen and then treated with a 10M solution of *n*-butyllithium in hexanes (2.3 mL, 23.16 mmol). The resulting reaction mixture was stirred at -78°C for 30 min and then treated dropwise with a solution of 4-(methylthio)phenylacetic acid (2.01 g, 11.03

20

propionamide (114 mg, 44%) as a white solid: mp 195-196°C; EI-HRMS m/e calcd for  $C_{18}H_{22}N_2OS_2$  ( $M^+$ ) 346.1174, found 346.1171.

### Example 10

#### 5 3-Cyclopentyl-N-thiazol-2-yl-2-(4-trifluoromethylsulfanyl-phenyl)-propionamide



A solution of diisopropylamine (2.4 mL, 16.80 mmol) in dry tetrahydrofuran (7.5 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (2.5 mL) was cooled to -78°C under nitrogen and then treated with a 2.5M solution of *n*-butyllithium in hexanes (6.7 mL, 16.80 mmol). The resulting reaction mixture was stirred at -78°C for 30 min and then treated dropwise with a solution of 4-(trifluoromethylthio)phenylacetic acid (1.89 g, 8.00 mmol) in dry tetrahydrofuran (7.5 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (2.5 mL). The reaction mixture was allowed to stir at -78°C for 55 min, at which time, a solution of iodomethylcyclopentane (1.85 g, 8.80 mmol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was allowed to warm to 25°C where it was stirred for 41 h. The reaction mixture was quenched with water and then concentrated *in vacuo* to remove tetrahydrofuran. The remaining aqueous phase was acidified to pH = 2 with a 10% aqueous hydrochloric acid solution and then extracted with ethyl acetate (300 mL). The organic layer was washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-trifluoromethylsulfanyl-phenyl)propionic acid (1.47 g, 58%) as a cream solid: mp 69-71°C; EI-HRMS m/e calcd for  $C_{15}H_{17}F_3O_2S$  ( $M^+$ ) 318.0901, found 318.0912.

mL, 16.80 mmol). The resulting reaction mixture was stirred at -78°C for 30 min and then treated dropwise with a solution of 4-(trifluoromethylthio)phenylacetic acid (1.89 g, 8.00 mmol) in dry tetrahydrofuran (7.5 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (2.5 mL). The reaction mixture was allowed to stir at -78°C for 55 min, at which time, a solution of iodomethylcyclopentane (1.85 g, 8.80 mmol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was allowed to warm to 25°C where it was stirred for 41 h. The reaction mixture was quenched with water and then concentrated *in vacuo* to remove tetrahydrofuran. The remaining aqueous phase was acidified to pH = 2 with a 10% aqueous hydrochloric acid solution and then extracted with ethyl acetate (300 mL). The organic layer was washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-trifluoromethylsulfanyl-phenyl)propionic acid (1.47 g, 58%) as a cream solid: mp 69-71°C; EI-HRMS *m/e* calcd for C<sub>15</sub>H<sub>17</sub>F<sub>3</sub>O<sub>2</sub>S (M<sup>+</sup>) 318.0901, found 318.0912.

A solution of 3-cyclopentyl-2-(4-trifluoromethylsulfanyl-phenyl)propionic acid (1.33 g, 4.18 mmol) in methanol (10 mL) was treated slowly with 4 drops of concentrated sulfuric acid. The resulting reaction mixture was heated under reflux for 36 h. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo* to remove methanol. The residue was diluted with ethyl acetate (200 mL). The organic phase was washed with a saturated aqueous sodium bicarbonate solution (1 x 100 mL), washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 97/3 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-trifluoromethylsulfanyl-phenyl)propionic acid methyl ester (1.37 g, 99%) as a light yellow oil: EI-HRMS *m/e* calcd for C<sub>16</sub>H<sub>19</sub>F<sub>3</sub>O<sub>2</sub>S (M<sup>+</sup>) 332.1058, found 332.1052.

A solution of 3-cyclopentyl-2-(4-trifluoromethanesulfonyl-phenyl)propionic acid (164.0 mg, 0.47 mmol) and triphenylphosphine (184.2 mg, 0.70 mmol) in methylene chloride (1.2 mL) was cooled to 0°C and then treated with *N*-bromosuccinimide (141.6 mg, 0.80 mmol) in small portions. After the complete addition of *N*-bromosuccinimide, the reaction mixture was allowed to warm to 25°C where it was stirred for 1 h. The reaction mixture was then treated with 2-aminothiazole (140.6 mg, 1.40 mmol). The resulting reaction mixture was stirred at 25°C for 22 h. The reaction mixture was then concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 3/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-N-thiazol-2-yl-2-(4-trifluoromethanesulfonyl-phenyl)-propionamide (47.9 mg, 24%) as a cream solid: mp 189-191°C; EI-HRMS *m/e* calcd for C<sub>18</sub>H<sub>19</sub>F<sub>3</sub>N<sub>2</sub>O<sub>3</sub>S<sub>2</sub> (M<sup>+</sup>) 432.0789, found 432.0791.

(B) In an analogous manner, there were obtained:

(a) From 3-cyclopentyl-2-(4-trifluoromethanesulfonyl-phenyl)propionic acid and 2-aminothiazole-4-carboxylic acid methyl ester: 2-[3-Cyclopentyl-2-(4-trifluoromethanesulfonyl-phenyl)-propionylamino]-thiazole-4-carboxylic acid methyl ester as a gray solid: mp 122-125°C; EI-HRMS *m/e* calcd for C<sub>20</sub>H<sub>21</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub>S<sub>2</sub> (M<sup>+</sup>) 490.0844, found 490.0844.

(b) From 3-cyclopentyl-2-(4-trifluoromethanesulfonyl-phenyl)propionic acid and 2-aminothiazole-4-carboxylic acid ethyl ester: 2-[3-Cyclopentyl-2-(4-trifluoromethanesulfonyl-phenyl)-propionylamino]-thiazole-4-carboxylic acid ethyl ester as a white solid: mp 132-134°C; EI-HRMS *m/e* calcd for C<sub>21</sub>H<sub>23</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub>S<sub>2</sub> (M<sup>+</sup>) 504.1000, found 504.0988.

(c) From 3-cyclopentyl-2-(4-trifluoromethanesulfonyl-phenyl)propionic acid and methyl 2-amino-4-thiazoleacetate: {2-[3-Cyclopentyl-2-(4-trifluoromethanesulfonyl-phenyl)-propionylamino]-thiazol-4-yl}-acetic acid methyl ester as a yellow foam: mp 48-52°C; EI-HRMS *m/e* calcd for C<sub>21</sub>H<sub>23</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub>S<sub>2</sub> (M<sup>+</sup>) 504.1000, found 504.0998.

mesh, 9/1 then 4/1 hexanes/ethyl acetate) afforded (3-chloro-4-methylsulfanyl-phenyl)-hydroxy-acetic acid ethyl ester (1.43 g, 38%) as a white solid: mp 56-57°C; EI-HRMS m/e calcd for  $C_{11}H_{13}ClO_3S$  ( $M^+$ ) 260.0273, found 260.0276.

- 5 A solution of (3-chloro-4-methylsulfanyl-phenyl)-hydroxy-acetic acid ethyl ester (1.43 g, 5.49 mmol) in pyridine (2 mL) was treated with acetic anhydride (2 mL) and 4-dimethylaminopyridine (50 mg, 0.41 mmol). The reaction mixture was stirred at 25°C for 16 h. The reaction mixture was then diluted with methylene chloride (100 mL). The organic layer was washed with a 1N aqueous hydrochloric acid solution (2 x 30 mL),  
10 washed with a saturated aqueous sodium chloride solution (1 x 30 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 4/1 hexanes/ethyl acetate) afforded acetoxy-(3-chloro-4-methylsulfanyl-phenyl)-acetic acid ethyl ester (1.51 g, 91%) as a light yellow oil: EI-HRMS m/e calcd for  $C_{13}H_{15}ClO_4S$  ( $M^+$ ) 302.0379, found 302.0387.

15

- A solution of acetoxy-(3-chloro-4-methylsulfanyl-phenyl)-acetic acid ethyl ester (1.47 g, 4.87 mmol) in hexamethylphosphoramide (7.2 mL) and methanol (20  $\mu$ L) was treated with a 0.1M solution of samarium iodide in tetrahydrofuran (146 mL, 14.6 mmol). The reaction mixture was stirred at 25°C under nitrogen for 6 min. During this time period,  
20 the reaction mixture changed from purple to white. The reaction mixture was diluted with water (150 mL) and then extracted with methylene chloride (3 x 100 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 4/1 hexanes/ethyl acetate) afforded (3-chloro-4-methylsulfanyl-phenyl)-acetic acid ethyl ester (0.71 g, 60%)  
25 as a light yellow oil: EI-HRMS m/e calcd for  $C_{11}H_{13}ClO_2S$  ( $M^+$ ) 244.0324, found 244.0332.

A solution of benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (0.62 g, 1.41 mmol) and 2-(3-chloro-4-methylsulfanyl-phenyl)-3-cyclopentyl-propionic acid (0.29 g, 0.95 mmol) in methylene chloride (10 mL) was treated with *N,N*-diisopropylethylamine (500  $\mu$ L, 2.87 mmol) and 2-aminothiazole (140 mg, 1.27mmol).  
5 The mixture was stirred under nitrogen at 25°C for 14 h. The reaction mixture was then washed with a 6N aqueous hydrochloric acid solution (1 x 15 mL) and washed with a saturated aqueous sodium chloride solution (1 x 25 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 4/1 hexanes/ethyl acetate) afforded 2-(3-chloro-4-  
10 methylsulfanyl-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide (0.26 g, 71%) as a white solid: EI-HRMS *m/e* calcd for  $C_{18}H_{21}ClN_2OS_2$  ( $M^+$ ) 380.0783, found 380.0792.

A solution of 2-(3-chloro-4-methylsulfanyl-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide (187 mg, 0.49 mmol) in methylene chloride (10 mL) was cooled to 0°C  
15 under nitrogen and then treated with 3-chloroperoxybenzoic acid (456.8 mg based on 50% purity). The reaction mixture was stirred for 3 h, and during this period, the temperature was allowed to warm to 25°C. The reaction mixture was then diluted with methylene chloride (50 mL). The organic layer was washed with a saturated aqueous sodium carbonate solution (1 x 20 mL), washed with a saturated aqueous sodium chloride  
20 solution (1 x 20 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 4/1 hexanes/ethyl acetate) afforded 2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide (102 mg, 50%) as a white solid: EI-HRMS *m/e* calcd for  $C_{18}H_{21}ClN_2O_3S_2$  ( $M^+$ ) 412.0682, found 412.0674.

mol) in a small amount of dry tetrahydrofuran was added slowly. The reaction mixture was then stirred at -78°C for 50 min, and then allowed to warm to 25°C, where it was stirred for 36 h. The reaction mixture was quenched with water (100 mL), and the resulting reaction mixture was concentrated *in vacuo* to remove tetrahydrofuran. The remaining residue was diluted with ethyl acetate (1.5 L). The organic phase was washed with a saturated aqueous sodium chloride solution (1 x 500 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-methanesulfonylphenyl)propionic acid methyl ester (41.79 g, 68%) as a yellow viscous oil: EI-HRMS *m/e* calcd for C<sub>16</sub>H<sub>22</sub>O<sub>4</sub>S (M<sup>+</sup>) 310.1239, found 310.1230.

A solution of 3-cyclopentyl-2-(4-methanesulfonylphenyl)propionic acid methyl ester (50.96 g, 0.16 mol) in methanol (410 mL) was treated with a 1N aqueous sodium hydroxide solution (345 mL, 0.35 mol). The reaction mixture was stirred at 25°C for 24 h. The reaction mixture was concentrated *in vacuo* to remove methanol. The resulting aqueous residue was acidified to pH = 2 with concentrated hydrochloric acid and then extracted with ethyl acetate (5 x 200 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford pure 3-cyclopentyl-2-(4-methanesulfonylphenyl)propionic acid (43.61 g, 90%) as a white solid which was used without further purification: mp 152-154°C; EI-HRMS *m/e* calcd for C<sub>15</sub>H<sub>20</sub>O<sub>4</sub>S (M<sup>+</sup>) 296.1082, found 296.1080.

Two separate reactions were setup in parallel: (1) A solution of (R)-(+)-4-benzyl-2-oxazolidinone (3.67 g, 20.73 mmol) in dry tetrahydrofuran (35 mL) was cooled to -78°C and then treated with a 2.5M solution of *n*-butyllithium in hexanes (7.9 mL, 19.86 mmol). The resulting reaction mixture was stirred at -78°C for 30 min and then allowed to warm to 25°C, where it was stirred for 1.5 h. (2) A solution of racemic 3-cyclopentyl-2-(4-methanesulfonylphenyl)propionic acid (5.12 g, 17.27 mmol) in dry tetrahydrofuran (35 mL) was cooled to 0°C and then treated with triethylamine (2.8 mL, 19.86 mmol). The

methanesulfonylphenyl)propionyl]-oxazolidin-2-one (3.84 g, 8.43 mmol) in tetrahydrofuran (33 mL) and water (11 mL). The reaction mixture was stirred 0°C for 1.5 h. The reaction mixture was then quenched with a 1.5N aqueous sodium sulfite solution (25 mL). The reaction mixture was further diluted with water (300 mL). The resulting aqueous layer was continuously extracted with diethyl ether until thin layer chromatography indicated the absence of the recovered chiral oxazolidinone in the aqueous layer. The aqueous layer was then acidified to pH = 2 with a 10% aqueous hydrochloric acid solution and extracted with ethyl acetate (300 mL). The organic extract was dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford (2R)-3-cyclopentyl-2-(4-methanesulfonylphenyl)propionic acid as a white solid (2.23 g, 89%) which was used without further purification. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 30/1 methylene chloride/methanol then 10/1 methylene chloride/methanol) was used to obtain a purified sample for analytical data and afforded pure (2R)-3-cyclopentyl-2-(4-methanesulfonylphenyl)propionic acid as a white foam: mp 62-64°C (foam to gel);  $[\alpha]_{589}^{23} = -50.0^\circ$  (c=0.02, chloroform); EI-HRMS m/e calcd for  $C_{15}H_{20}O_4S$  ( $M^+$ ) 296.1082, found 296.1080.

A solution of triphenylphosphine (3.35 g, 12.79 mmol) in methylene chloride (19 mL) was cooled to 0°C and then slowly treated with *N*-bromosuccinimide (2.28 g, 12.79 mmol) in small portions. The reaction mixture was stirred at 0°C for 30 min, and during this time period, the color of the reaction mixture changed from light yellow to a darker yellow then to a purple color. The cooled purple reaction mixture was then treated with the (2R)-3-cyclopentyl-2-(4-methanesulfonylphenyl)propionic acid (2.23 g, 7.52 mmol). The resulting reaction mixture was then allowed to warm to 25°C over 45 min, at which time, the reaction mixture was then treated with 2-aminothiazole (1.88 g, 18.81 mmol). The resulting reaction mixture was stirred at 25°C for 12 h. The reaction mixture was then concentrated *in vacuo* to remove methylene chloride. The remaining black residue was diluted with ethyl acetate (300 mL) and then washed well with a 10% aqueous hydrochloric acid solution (2 x 100 mL), a 5% aqueous sodium bicarbonate solution (3 x

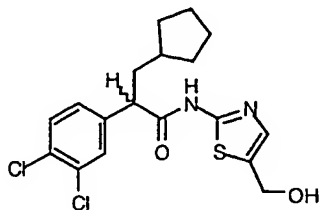


20 min and then slowly treated with a solution of 4-chloro-3-nitrophenylacetic acid methyl ester (5.00 g, 21.8 mmol) in a small amount of tetrahydrofuran over a 15 min period. The reaction mixture turned deep purple (almost black) in color. The reaction mixture was then stirred at -78°C for 1 h, at which time, a solution of  
5 iodomethylcyclopentane (4.58 g, 21.8 mol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was then stirred at -78°C and then allowed to warm to 25°C, where it was stirred for 48 h. The reaction mixture was quenched with a saturated aqueous ammonium chloride solution (50 mL), and the resulting reaction mixture was concentrated *in vacuo* to remove tetrahydrofuran. The remaining residue  
10 was diluted with ethyl acetate (150 mL) and water (50 mL). The organic phase was washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 4/1 hexanes/ethyl acetate) afforded 2-(4-chloro-3-nitrophenyl)-3-cyclopentyl-propionic acid methyl ester (2.17 g, 32%) as a yellow oil: EI-HRMS *m/e* calcd for  
15  $C_{15}H_{18}ClNO_4$  ( $M^+$ ) 311.0924, found 311.0927.

A solution of 2-(4-chloro-3-nitrophenyl)-3-cyclopentyl-propionic acid methyl ester (1.00 g, 3.21 mmol) and sodium methanesulfinate (0.36 g, 3.53 mmol) in dimethyl sulfoxide (3 mL) was heated at 130°C for 5 h. The black reaction mixture was then poured over ice  
20 (20 g), resulting in the formation of a brown sticky substance. The resulting mixture was then treated with ethyl acetate (50 mL) and water (50 mL), and the layers were separated. The aqueous layer was further extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck  
25 Silica gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-propionic acid methyl ester (0.95 g, 84%) as a yellow gel: FAB-HRMS *m/e* calcd for  $C_{16}H_{21}NO_6S$  ( $M+H$ )<sup>+</sup> 356.1169, found 356.1175.

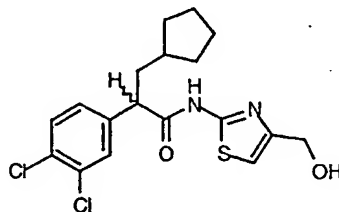
## Example 15

## 3-Cyclopentyl-2-(3,4-dichlorophenyl)-N-(5-hydroxymethyl-thiazol-2-yl)-propionamide



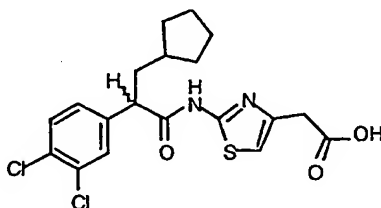
- 5 A solution of 2-[3-cyclopentyl-2-(3,4-dichlorophenyl)-propionylamino]-thiazole-5-carboxylic acid ethyl ester (prepared in Example 1 (B)(g), 110 mg, 0.25 mmol) in diethyl ether (2 mL) at 0°C was slowly treated with lithium aluminum hydride (12 mg, 0.31 mmol). The resulting reaction mixture continued to stir at 0°C and was allowed to gradually warm to 25°C. The reaction mixture was then stirred at 25°C over a period of
- 10 14 h. The reaction mixture was slowly quenched by the dropwise addition of water (5 mL). The resulting reaction mixture was partitioned between water and ethyl acetate. A saturated aqueous sodium chloride solution was added to break up the emulsions. The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/3 hexanes/ethyl acetate)
- 15 afforded 3-cyclopentyl-2-(3,4-dichlorophenyl)-N-(5-hydroxymethyl-thiazol-2-yl)-propionamide (52.9 mg, 53%) as a light yellow solid: mp 128-130°C; EI-HRMS *m/e* calcd for C<sub>18</sub>H<sub>20</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>2</sub>S (M<sup>+</sup>) 398.0623, found 398.0623.

## Example 17

**3-Cyclopentyl-2-(3,4-dichlorophenyl)-N-(4-hydroxymethyl-thiazol-2-yl)-propionamide**

- 5 A solution of 2-[3-cyclopentyl-2-(3,4-dichlorophenyl)-propionylamino]-thiazole-4-carboxylic acid ethyl ester (prepared in Example 1(B)(f), 200 mg, 0.45 mmol) in tetrahydrofuran (3 mL) at 25°C was slowly treated with sodium borohydride (26.0 mg, 0.68 mmol). The reaction mixture was heated under reflux for 48 h. The reaction mixture was allowed to cool to 25°C and then slowly quenched by the dropwise addition
- 10 of water. The resulting reaction mixture was partitioned between water and ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(3,4-dichlorophenyl)-N-(4-hydroxymethyl-thiazol-2-yl)-propionamide (44.9 mg, 25%) as a white solid: mp 88-90°C; EI-HRMS *m/e* calcd for
- 15  $C_{18}H_{20}Cl_2N_2O_2S$  ( $M^+$ ) 398.0623, found 398.0631.

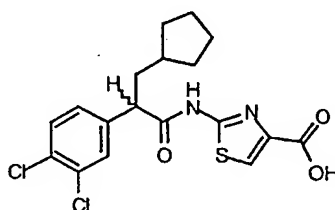
## Example 18

**{2-[3-Cyclopentyl-2-(3,4-dichlorophenyl)-propionylamino]-thiazol-4-yl}-acetic acid**

propionylamino]-thiazole-5-carboxylic acid (210 mg, 22%) as a white solid: mp 269-270°C; FAB-HRMS m/e calcd for  $C_{18}H_{18}Cl_2N_2O_3S$  (M+H)<sup>+</sup> 413.0493, found 413.0483.

### Example 20

#### 5 2-[3-Cyclopentyl-2-(3,4-dichlorophenyl)-propionylamino]-thiazole-4-carboxylic acid

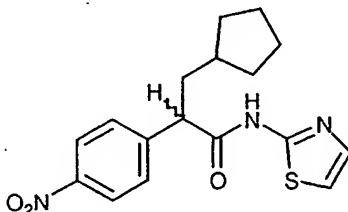


A solution of 2-[3-cyclopentyl-2-(3,4-dichlorophenyl)-propionylamino]-thiazole-4-carboxylic acid ethyl ester (prepared in Example 1(B)(f), 600 mg, 1.36 mmol) in absolute ethanol (6 mL) was treated with a 1N aqueous sodium hydroxide solution (2.85 mL, 2.85 mmol). The reaction mixture was heated under reflux for 15 h. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo* to remove absolute ethanol. The resulting yellow residue was acidified to pH = 2 with concentrated hydrochloric acid and extracted with ethyl acetate (2 x 100 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Precipitation from 1/1 hexanes/ethyl acetate afforded 2-[3-cyclopentyl-2-(3,4-dichlorophenyl)-propionylamino]-thiazole-4-carboxylic acid (399 mg, 71%) as a white solid: mp 285-287°C; FAB-HRMS m/e calcd for  $C_{18}H_{18}Cl_2N_2O_3S$  (M+H)<sup>+</sup> 413.0493, found 413.0481.

propionylamino]-thiazole-5-carboxylic acid methyl ester as a white solid: mp 150-151°C; FAB-HRMS m/e calcd for  $C_{19}H_{20}Cl_2N_2O_3S$  (M+H)<sup>+</sup> 427.0650, found 427.0650.

### Example 22

#### 5 (A) 3-Cyclopentyl-2-(4-nitro-phenyl)-N-thiazol-2-yl-propionamide

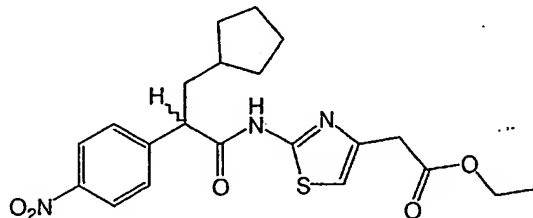


A solution of freshly prepared lithium diisopropylamide (430.55 mL of a 0.3M stock solution, 129.16 mmol) cooled to -78°C was treated with (4-nitro-phenyl)-acetic acid ethyl ester (26.32 g, 125.83 mmol) in tetrahydrofuran/hexamethylphosphoramide (312.5 mL, 3:1). The resulting solution was stirred at -78°C for 45 min. Iodomethylcyclopentane (27.75 g, 132.1 mmol) was then added in hexamethylphosphoramide (27.75 mL). The mixture was stirred at -78°C for 4 h. The reaction was then warmed to 25°C and was stirred at 25°C for 16 h. The reaction mixture was then quenched by the dropwise addition of a saturated aqueous ammonium chloride solution (250 mL). This mixture was concentrated, diluted with water (250 mL), and extracted with ethyl acetate (3 x 300 mL). The organics were washed with a saturated aqueous lithium chloride solution (2 x 250 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 98/2 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-nitro-phenyl)-propionic acid ethyl ester (28.30 g, 77.2%) as a yellow oil: EI-HRMS m/e calcd for  $C_{16}H_{21}NO_4$  (M<sup>+</sup>) 291.1470, found 291.1470.

A solution of 3-cyclopentyl-2-(4-nitro-phenyl)-propionic acid ethyl ester (14.1 g, 48.06 mmol) in tetrahydrofuran/water (300 mL, 3:1) was treated with lithium hydroxide (4.35 g,

## Example 23

## {2-[3-Cyclopentyl-2-(4-nitro-phenyl)-propionylamino]-thiazol-4-yl}-acetic acid ethyl ester

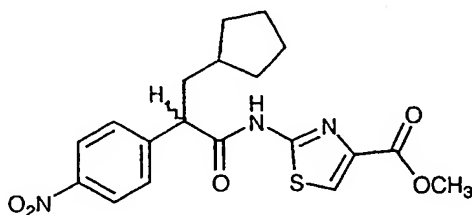


- 5 A solution of 3-cyclopentyl-2-(4-nitro-phenyl)-propionic acid (prepared in Example 22A, 263.0 mg, 1.0 mmol) in *N,N*-dimethylformamide (10 mL) was treated with *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (379 mg, 1.0 mmol), (2-amino-thiazol-4-yl)-acetic acid ethyl ester (279 mg, 1.5 mmol) and *N,N*-diisopropylethylamine (0.34 mL, 2.0 mmol). The reaction mixture was stirred at 25°C for
- 10 5 h. The reaction mixture was then poured into a 2N aqueous hydrochloric acid solution (25 mL) and extracted with ethyl acetate (3 x 25 mL). The organic layers were combined and washed with water (1 x 75 mL), a saturated aqueous sodium bicarbonate solution (1 x 75 mL), a saturated aqueous sodium chloride solution (3 x 75 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60,
- 15 230-400 mesh, 70/30 hexanes/ethyl acetate) afforded {2-[3-cyclopentyl-2-(4-nitro-phenyl)-propionylamino]-thiazol-4-yl}-acetic acid ethyl ester (70.0 mg, 39.4%) as a pale yellow oil: FAB-HRMS *m/e* calcd for C<sub>21</sub>H<sub>25</sub>N<sub>3</sub>O<sub>5</sub>S (M+H)<sup>+</sup> 432.1593, found 432.1595.

under hydrogen gas at 60 psi at 25°C for 4 h. The catalyst was then filtered off through a pad of celite (ethyl acetate). The filtrate was concentrated *in vacuo* to give {2-[2-(4-amino-phenyl)-3-cyclopentyl-propionylamino]-thiazol-4-yl}-acetic acid methyl ester (64.5 mg, 93.3%) as a tan oil: EI-HRMS *m/e* calcd for C<sub>20</sub>H<sub>25</sub>N<sub>3</sub>O<sub>3</sub>S (M<sup>+</sup>) 387.1616, found 387.1612.

### Example 26

#### 2-[3-Cyclopentyl-2-(4-nitro-phenyl)-propionylamino]-thiazole-4-carboxylic acid methyl ester



10

A solution of 2-[3-cyclopentyl-2-(4-nitro-phenyl)-propionylamino]-thiazole-4-carboxylic acid ethyl ester (prepared in Example 39(B)(b), 135 mg, 0.32 mmol) in methanol (10 mL) was treated with a catalytic amount of sulfuric acid. The reaction mixture was refluxed for 68 h. The reaction was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate) afforded 2-[3-cyclopentyl-2-(4-nitro-phenyl)-propionylamino]-thiazole-4-carboxylic acid methyl ester (71.4 mg, 54.8%) as a pale yellow solid: EI-HRMS *m/e* calcd for C<sub>19</sub>H<sub>21</sub>N<sub>3</sub>O<sub>5</sub>S (M<sup>+</sup>) 403.1201, found 403.1188.

15

(49.7 mL, 3:1). The resulting reaction solution was stirred at -78°C for 1 h. Iodomethylcyclopentane (4.64 g, 22.08 mmol) was then added in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (4.64 mL). The reaction mixture was stirred at -78°C for 4 h. The reaction was then warmed to 25°C and was stirred at 25°C for 48 h. The solution was then quenched by the slow addition of the reaction mixture to a 2N aqueous hydrochloric acid solution (50 mL). The product was extracted into ethyl acetate (1 x 150 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 85/15 hexanes/ethyl acetate) afforded 2-(3-chloro-phenyl)-3-cyclopentyl-propionic acid (3.68 g, 72.9%) as a yellow solid: mp 70-72°C; EI-HRMS *m/e* calcd for C<sub>14</sub>H<sub>17</sub>ClO<sub>2</sub> (M<sup>+</sup>) 252.0917, found 252.0915.

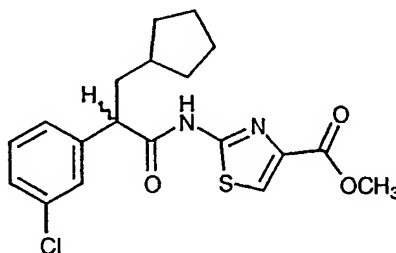
A solution of 2-(3-chloro-phenyl)-3-cyclopentyl-propionic acid (252 mg, 1.0 mmol) in methylene chloride (10 mL) was cooled to 0°C and then treated with a 2.0M solution oxalyl chloride in methylene chloride (0.6 mL, 1.2 mmol) and a few drops of *N,N*-dimethylformamide. The reaction mixture was stirred at 0°C for 15 min and at 25°C for 2 h. The reaction mixture was then treated with (2-amino-thiazol-4-yl)-acetic acid ethyl ester (409 mg, 2.2 mmol) and *N,N*-diisopropylethylamine (0.5 mL, 2.4 mmol). This solution was stirred at 25°C for 48 h. At this time, the reaction was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 80/20 hexanes/ethyl acetate) afforded {2-[2-(3-chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazol-4-yl}-acetic acid ethyl ester (254 mg, 60.3%) as a white solid: mp 121-125°C; EI-HRMS *m/e* calcd for C<sub>21</sub>H<sub>25</sub>ClN<sub>2</sub>O<sub>3</sub>S (M<sup>+</sup>) 420.1274, found 420.1268.

(B) In an analogous manner, there were obtained:

- (a) From 2-amino-thiazole-4-carboxylic acid ethyl ester and 2-(3-chloro-phenyl)-3-cyclopentyl-propionic acid: 2-[2-(3-Chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazole-4-carboxylic acid ethyl ester as a white solid: mp 167-168°C; EI-HRMS *m/e* calcd for C<sub>20</sub>H<sub>23</sub>ClN<sub>2</sub>O<sub>3</sub>S (M<sup>+</sup>) 406.1117, found 406.1103.



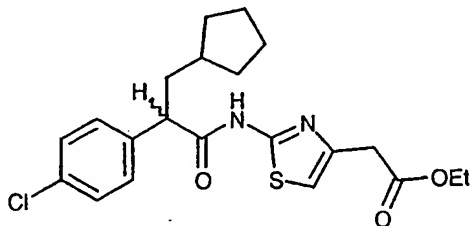
## Example 30

2-[2-(3-Chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazole-4-carboxylic acid  
methyl ester

- 5 A solution of 2-[2-(3-chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazole-4-carboxylic acid ethyl ester (prepared in Example 28(B)(a), 94.5 mg, 0.23 mmol) in methanol (15 mL) was treated with a catalytic amount of sulfuric acid. The reaction mixture was refluxed for 40 h. The reaction was then concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 75/25 hexanes/ethyl acetate)
- 10 afforded 2-[2-(3-chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazole-4-carboxylic acid methyl ester (36.8 mg, 40.3%) as a white solid: mp 95-98°C; EI-HRMS *m/e* calcd for  $C_{19}H_{21}ClN_2O_3S$  ( $M^+$ ) 392.0961, found 392.0989.

## Example 31

- 15 (A) {2-[2-(4-Chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazol-4-yl}-acetic acid ethyl ester



A solution of freshly prepared lithium diisopropylamide (78.0 mL of a 0.91M stock solution, 70.98 mmol) cooled to -78°C was treated with (4-chloro-phenyl)-acetic acid

thiazole-4-carboxylic acid ethyl ester as a white solid: mp 114-116°C; EI-HRMS m/e calcd for  $C_{20}H_{23}ClN_2O_3S$  ( $M^+$ ) 406.1117, found 406.1119.

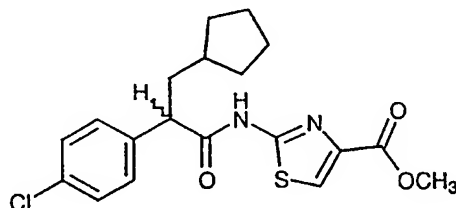
(b) From 2-amino-pyridine and 2-(4-chloro-phenyl)-3-cyclopentyl-propionic acid: 2-(4-Chloro-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide as a clear oil: EI-HRMS m/e calcd for  $C_{19}H_{21}ClN_2O$  ( $M^+$ ) 328.1342, found 328.1355.

(c) From 6-amino-nicotinic acid methyl ester and 2-(4-chloro-phenyl)-3-cyclopentyl-propionic acid: 6-[2-(4-Chloro-phenyl)-3-cyclopentyl-propionylamino]-nicotinic acid methyl ester as a white foam: EI-HRMS m/e calcd for  $C_{21}H_{23}ClN_2O_3$  ( $M^+$ ) 386.1397, found 386.1384.

10

### Example 32

2-[2-(4-Chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazole-4-carboxylic acid methyl ester:

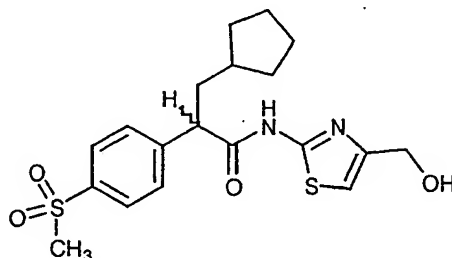


15 A solution of 2-[2-(4-chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazole-4-carboxylic acid ethyl ester (prepared in Example 31(B)(a), 105 mg, 0.25 mmol) in methanol (10 mL) was treated with a catalytic amount of sulfuric acid. The reaction mixture was refluxed for 68 h. The reaction was concentrated *in vacuo*. High pressure liquid chromatography (Chromegasphere SI-60, 10  $\mu$ m, 60 Å, 25 cm X 23 cm ID, 75/25  
20 heptane/ethyl acetate) afforded 2-[2-(4-chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazole-4-carboxylic acid methyl ester (41.3 mg, 40.7%) as a white solid: mp 156-157°C; EI-HRMS m/e calcd for  $C_{19}H_{21}ClN_2O_3S$  ( $M^+$ ) 392.0961, found 392.0956.

for 2 h. The reaction was then quenched by the dropwise addition of water. The reaction was then diluted with more water (25 mL) and extracted with ethyl acetate (3 x 25 mL). The organics were dried over sodium sulfate, filtered and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 75/25 hexanes/ethyl acetate) afforded  
5 2-(4-chloro-phenyl)-3-cyclopentyl-N-(5-hydroxymethyl-thiazol-2-yl)-propionamide (63.4 mg, 55.4%) as a white solid: mp 115-117°C; EI-HRMS m/e calcd for  $C_{18}H_{21}ClN_2O_2S$  ( $M^+$ ) 364.1012, found 364.1004.

### Example 35

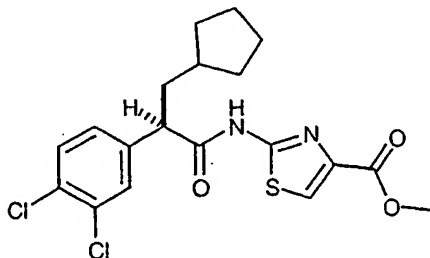
10 3-Cyclopentyl-N-(4-hydroxymethyl-thiazol-2-yl)-2-(4-methanesulfonyl-phenyl)-propionamide



A solution of 2-[3-cyclopentyl-2-(4-methanesulfonyl-phenyl)-propionylamino]-thiazole-4-carboxylic acid ethyl ester (prepared in Example 3(B)(b), 130 mg, 0.29 mmol) in  
15 diethyl ether (2 mL) was cooled to 0°C and then slowly treated with lithium aluminum hydride (17 mg, 0.44 mmol). The reaction mixture was allowed to warm to 25°C where it was stirred for 4 h. After 4 h at 25°C, thin layer chromatography indicated the presence of starting material. An additional amount of lithium aluminum hydride (11 mg, 0.29 mmol) was added to the reaction mixture, and the reaction mixture was allowed to stir at  
20 25°C for 15 h. The reaction mixture was then slowly quenched by the dropwise addition of water. The resulting mixture was partitioned between water and ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, ethyl acetate) afforded 3-cyclopentyl-N-(4-hydroxymethyl-thiazol-2-yl)-2-(4-methanesulfonyl-phenyl)-

## Example 37

## (2R)-2-[3-Cyclopentyl-2-(3,4-dichloro-phenyl)-propionylamino]-thiazole-4-carboxylic acid methyl ester



- 5 A solution triphenylphosphine (164 mg, 0.63 mmol) in methylene chloride (3 mL) was cooled to 0°C and then treated with *N*-bromosuccinimide (112 mg, 0.63 mmol) in small portions. The resulting orange reaction mixture was stirred at 0°C for 20 min and then treated with (2R)-3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionic acid (prepared in Example 54, 150 mg, 0.52 mmol). The reaction mixture was stirred at 0°C for an additional 15 min and then allowed to warm to 25°C. The reaction mixture was then treated with 2-aminothiazole-4-carboxylic acid methyl ester (181 mg, 1.15 mmol). The resulting reaction mixture was stirred at 25°C for 15 h. The crude reaction mixture was directly purified by flash chromatography (Merck Silica gel 60, 230-400 mesh, 3/1 hexanes/ethyl acetate) to afford impure (2R)-2-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionylamino]-thiazole-4-carboxylic acid methyl ester. The impure product was diluted with ethyl acetate and then washed with a saturated aqueous sodium bicarbonate solution. The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo* to provide pure (2R)-2-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionylamino]-thiazole-4-carboxylic acid methyl ester (92 mg, 41%) as a white solid: mp 143-144°C;  $[\alpha]^{23}_{589} = -10.2^\circ$  (c=0.98, chloroform); EI-HRMS *m/e* calcd for C<sub>19</sub>H<sub>20</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>3</sub>S (M<sup>+</sup>) 426.0572, found 426.0562.
- 10
- 15
- 20

stirred at -78°C for 1 h. The reaction mixture was then allowed to warm to 25°C, where it was stirred for 14 h. The reaction mixture was then acidified to pH = 2 by the dropwise addition of a 1N aqueous hydrochloric acid solution and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, chloroform then 99/1 chloroform/methanol) afforded 3-cyclopentyl-2-(3,4-dichlorophenyl)-propionic acid (10.28 g, 81%) as a white solid: mp 74.5-76.9°C; EI-HRMS m/e calcd for C<sub>14</sub>H<sub>16</sub>Cl<sub>2</sub>O<sub>2</sub> (M<sup>+</sup>) 286.0527, found 286.0534.

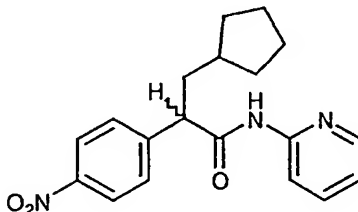
10 A solution of 3-cyclopentyl-2-(3,4-dichlorophenyl)-propionic acid (114 mg, 0.39 mmol) in methylene chloride (10 mL) was treated with 1 drop of *N,N*-dimethylformamide and then cooled to 0°C. The reaction mixture was then treated with a 2.0M solution of oxalyl chloride in methylene chloride (0.22 mL, 0.44 mmol). The reaction mixture was stirred at 0°C for 30 min and then treated with a solution of 2-aminopyridine (78 mg, 0.83 mmol) and *N,N*-diisopropylethylamine (0.16 mL, 0.95 mmol) in tetrahydrofuran (2 mL). The resulting reaction mixture was stirred at 25°C for 14 h. The reaction mixture was then diluted with water (10 mL) and extracted with methylene chloride (2 x 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, hexanes then 19/1 to 20 4/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(3,4-dichloro-phenyl)-N-pyridin-2-yl-propionamide (58 mg, 50%) as a white foam: EI-HRMS m/e calcd for C<sub>19</sub>H<sub>20</sub>Cl<sub>2</sub>N<sub>2</sub>O (M<sup>+</sup>) 362.0953, found 362.0955.

(B) In an analogous manner, there were obtained:

25 (a) From 2-amino-5-nitropyridine and 3-cyclopentyl-2-(3,4-dichlorophenyl)-propionic acid: 3-Cyclopentyl-2-(3,4-dichloro-phenyl)-N-(5-nitropyridin)-2-yl-propionamide as a yellow-orange foam: EI-HRMS m/e calcd for C<sub>19</sub>H<sub>19</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>3</sub> (M<sup>+</sup>) 407.0803, found 407.0799.

## Example 39

## (A) 3-Cyclopentyl-2-(4-nitro-phenyl)-N-pyridin-2-yl-propionamide



A solution of 3-cyclopentyl-2-(4-nitro-phenyl)-propionic acid (prepared in Example 22,  
5 263 mg, 1.0 mmol) in methylene chloride (5 mL) was cooled to 0°C and then treated with  
a 2.0M solution of oxalyl chloride in methylene chloride (0.6 mL, 1.2 mmol) and a few  
drops of *N,N*-dimethylformamide. The reaction mixture was stirred at 0°C for 15 min  
and then at 25°C for 1 h. The reaction mixture was then treated with a solution of 2-  
aminopyridine (207 mg, 2.2 mmol) in tetrahydrofuran (5 mL) and *N,N*-  
10 diisopropylethylamine (0.42 mL, 2.5 mmol). The reaction mixture was stirred at 25°C for  
24 h. At this time, the reaction was concentrated *in vacuo*. Flash chromatography  
(Merck Silica gel 60, 230-400 mesh, 80/20 hexanes/ethyl acetate) afforded 3-cyclopentyl-  
2-(4-nitro-phenyl)-N-pyridin-2-yl-propionamide (110.2 mg, 32.5%) as a white solid: mp  
152-154°C; EI-HRMS *m/e* calcd for C<sub>19</sub>H<sub>21</sub>N<sub>3</sub>O<sub>3</sub> (M<sup>+</sup>) 339.1582, found 339.1581.

15

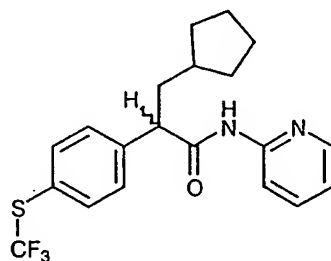
(B) In an analogous manner, there were obtained:

- (a) From 4-aminopyrimidine and 3-cyclopentyl-2-(4-nitro-phenyl)-propionic acid: 3-  
Cyclopentyl-2-(4-nitro-phenyl)-N-pyrimidin-4-yl-propionamide as a white solid: mp 152-  
153°C; EI-HRMS *m/e* calcd for C<sub>18</sub>H<sub>20</sub>N<sub>4</sub>O<sub>3</sub> (M<sup>+</sup>) 340.1535, found 340.1533.
- 20 (b) From 2-amino-thiazole-4-carboxylic acid ethyl ester and 3-cyclopentyl-2-(4-nitro-  
phenyl)-propionic acid: 2-[3-Cyclopentyl-2-(4-nitro-phenyl)-propionylamino]-thiazole-4-  
carboxylic acid ethyl ester as a pale yellow solid: mp 110-115°C; EI-HRMS *m/e* calcd for  
C<sub>20</sub>H<sub>23</sub>N<sub>3</sub>O<sub>5</sub>S (M<sup>+</sup>) 417.1358, found 417.1346.

cooled to 0°C and then treated with *N*-bromosuccinimide (150 mg, 0.84 mmol) in small portions. After the complete addition of *N*-bromosuccinimide, the reaction mixture was allowed to warm to 25°C over 30 min. The orange reaction mixture was then treated with 2-aminopyridine (151 mg, 1.60 mmol), and the resulting reaction mixture was stirred at  
5 25°C for 15 h. The reaction mixture was then concentrated *in vacuo* to remove methylene chloride. The remaining residue was partitioned between water and ethyl acetate. The organic layer was washed with a 1N aqueous hydrochloric acid solution, washed with a saturated aqueous sodium bicarbonate solution, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh,  
10 3/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-methylsulfanyl-phenyl)-*N*-pyridin-2-yl-propionamide (83 mg, 32%) as a white solid: mp 127-128°C; EI-HRMS *m/e* calcd for C<sub>20</sub>H<sub>24</sub>N<sub>2</sub>OS (M<sup>+</sup>) 340.1609, found 340.1611.

#### Example 41

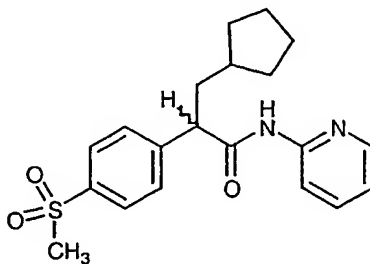
15 3-Cyclopentyl-*N*-pyridin-2-yl-2-(4-trifluoromethylsulfanyl-phenyl)-propionamide



A solution of diisopropylamine (2.4 mL, 16.80 mmol) in dry tetrahydrofuran (7.5 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (2.5 mL) was cooled to -78°C under nitrogen and then treated with a 2.5M solution of *n*-butyllithium in hexanes (6.7  
20 mL, 16.80 mmol). The resulting reaction mixture was stirred at -78°C for 30 min and then treated dropwise with a solution of 4-(trifluoromethylthio)phenylacetic acid (1.89 g, 8.00 mmol) in dry tetrahydrofuran (7.5 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (2.5 mL). The reaction mixture was allowed to stir at -78°C for 55 min, at which time, a solution of iodomethylcyclopentane (1.85 g, 8.80 mmol) in a small amount

## Example 42

## 3-Cyclopentyl-2-(4-methanesulfonyl-phenyl)-N-pyridin-2-yl-propionamide



A solution of 2-aminopyridine (95 mg, 1.01 mmol) in acetonitrile (2 mL) was treated with  
5 3-cyclopentyl-2-(4-methanesulfonyl-phenyl)propionic acid (prepared in Example 3(A),  
250 mg, 0.84 mmol), triphenylphosphine (243 mg, 0.93 mmol), triethylamine (350  $\mu$ L,  
2.53 mmol), and carbon tetrachloride (1 mL). The resulting reaction mixture was stirred  
at 25°C for 15 h. The cloudy reaction mixture was diluted with water and then extracted  
with methylene chloride. The organic layer was dried over magnesium sulfate, filtered,  
10 and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh,  
1/3 hexanes/ethyl acetate) afforded impure 3-cyclopentyl-2-(4-methanesulfonyl-phenyl)-  
N-pyridin-2-yl-propionamide. Recrystallization from hexanes/methylene chloride  
provided pure 3-cyclopentyl-2-(4-methanesulfonyl-phenyl)-N-pyridin-2-yl-propionamide  
(170 mg, 54%) as a white solid: mp 172-173°C; EI-HRMS *m/e* calcd for  $C_{20}H_{24}N_2O_3S$   
15 ( $M^+$ ) 372.1508, found 372.1498.



A solution of 3-cyclopentyl-2-(4-trifluoromethylsulfanyl-phenyl)propionic acid (1.33 g, 4.18 mmol) in methanol (10 mL) was treated slowly with 4 drops of concentrated sulfuric acid. The resulting reaction mixture was heated under reflux for 36 h. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo* to remove methanol.

5 The residue was diluted with ethyl acetate (200 mL). The organic phase was washed with a saturated aqueous sodium bicarbonate solution (1 x 100 mL), washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 97/3 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-trifluoromethylsulfanyl-phenyl)propionic acid methyl ester (1.37 g, 99%) as a light yellow oil: EI-HRMS *m/e*

10 calcd for  $C_{16}H_{19}F_3O_2S$  ( $M^+$ ) 332.1058, found 332.1052.

A solution of 3-cyclopentyl-2-(4-trifluoromethylsulfanyl-phenyl)propionic acid methyl ester (1.14 g, 3.43 mmol) in methylene chloride (8.6 mL) was treated with 3-chloroperoxybenzoic acid (80-85% grade, 2.00 g based on 80%, 9.26 mmol). The

15 reaction mixture was stirred at 25°C for 17 h, at which time, thin layer chromatography showed the presence of two new lower  $R_f$  products. An additional 2.00 g of 3-chloroperoxybenzoic acid was added to the reaction mixture to drive the conversion of the sulfoxide to the sulfone, and the resulting reaction mixture was stirred at 25°C for 3 d.

20 The reaction mixture was concentrated *in vacuo* to remove methylene chloride. The resulting residue was diluted with ethyl acetate (300 mL). The organic phase was washed with a saturated aqueous sodium bicarbonate solution (3 x 100 mL), washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230

25 mesh, 19/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-trifluoromethanesulfonyl-phenyl)propionic acid methyl ester (1.19 g, 95%) as a light yellow oil: EI-HRMS *m/e* calcd for  $C_{16}H_{19}F_3O_4S$  ( $M^+$ ) 364.0956, found 364.0965.

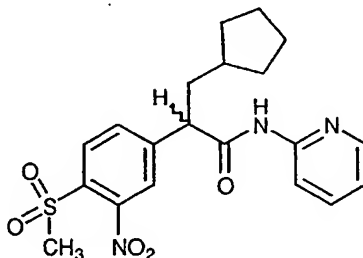
(b) From 3-cyclopentyl-2-(4-trifluoromethanesulfonyl-phenyl)propionic acid and 2-amino-5-methyl pyridine: 3-Cyclopentyl-N-(5-methyl-pyridin-2-yl)-2-(4-trifluoromethanesulfonyl-phenyl)-propionamide as a pale yellow solid: mp 155-157°C; EI-HRMS m/e calcd for  $C_{21}H_{23}F_3N_2O_3S$  ( $M^+$ ) 440.1381, found 440.1376.

- 5 (c) From 3-cyclopentyl-2-(4-trifluoromethanesulfonyl-phenyl)propionic acid and 6-aminonicotinic acid methyl ester: 6-[3-Cyclopentyl-2-(4-trifluoromethanesulfonyl-phenyl)-propionylamino]-nicotinic acid methyl ester as a yellow foam: mp 58-62°C; EI-HRMS m/e calcd for  $C_{22}H_{23}F_3N_2O_5S$  ( $M^+$ ) 484.1280, found 484.1274.

10

#### Example 44

##### 3-Cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-N-pyridin-2-yl-propionamide



- A solution of 4-chloro-3-nitrophenylacetamide (2.00 g, 9.32 mmol) in methanol (40 mL) was treated with Amberlyst® 15 ion exchange resin (15.00 g). The resulting reaction mixture was heated under reflux for 64 h. The reaction mixture was allowed to cool to 25°C and then filtered to remove the Amberlyst® 15 ion exchange resin. The filtrate was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 3/1 hexanes/ethyl acetate) afforded 4-chloro-3-nitrophenylacetic acid methyl ester (1.91 g, 89%) as a yellow oil: EI-HRMS m/e calcd for  $C_9H_8ClNO_4$  ( $M^+$ ) 229.0142, found 229.0146.

20

A solution of diisopropylamine (3.35 mL, 23.9 mmol) in dry tetrahydrofuran (45 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (15 mL) was cooled to -78°C and

A solution of 3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-propionic acid methyl ester (865 mg, 2.43 mmol) in tetrahydrofuran (6 mL) was treated with a 0.8M aqueous lithium hydroxide solution (4.6 mL, 3.65 mmol). The reaction mixture was stirred at 25°C for 3 h. The reaction mixture was concentrated *in vacuo* to remove tetrahydrofuran. The resulting aqueous residue was diluted with water (25 mL) and then treated with a 1N aqueous hydrochloric acid solution (10 mL). The resulting aqueous layer was then extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/4 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-propionic acid (723 mg, 87%) as a white foam. Analytical data indicated the presence of a small impurity; however, the 3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-propionic acid was used without further purification in subsequent reactions.

15

A solution of triphenylphosphine (138 mg, 0.53 mmol) in methylene chloride (2 mL) was cooled to 0°C and then slowly treated with *N*-bromosuccinimide (94 mg, 0.53 mmol) in small portions. The reaction mixture was stirred at 0°C for 10 min and then treated with 3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-propionic acid (150 mg, 0.44 mmol). The resulting reaction mixture was stirred at 0°C for 5 min and then allowed to warm to 25°C, where it was stirred for 25 min. The reaction mixture was then treated with 2-aminopyridine (91 mg, 0.97 mmol). The resulting reaction mixture was stirred at 25°C for 15 h. The crude reaction mixture was directly purified by flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate) to afford 3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-*N*-pyridin-2-yl-propionamide (106 mg, 58%) as a white foam: mp 92-95°C (foam to gel); FAB-HRMS *m/e* calcd for C<sub>20</sub>H<sub>23</sub>N<sub>3</sub>O<sub>5</sub>S (M+H)<sup>+</sup> 418.1436, found 418.1430.

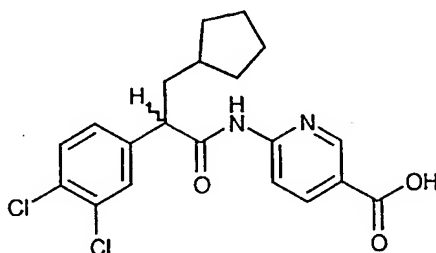
25

6-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionylamino]-nicotinic acid methyl ester (1.10 g, 84%) as a white foam:  $[\alpha]_{589}^{23} = -68.0^\circ$  ( $c=0.128$ , chloroform); FAB-HRMS  $m/e$  calcd for  $C_{21}H_{22}Cl_2N_2O_3$  ( $M+H$ )<sup>+</sup> 421.1086, found 421.1079.

5

## Example 46

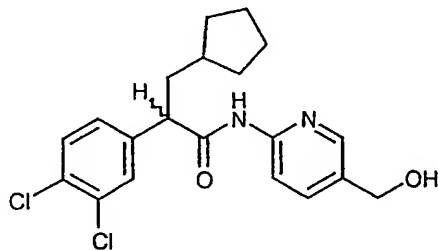
## 6-[3-Cyclopentyl-2-(3,4-dichloro-phenyl)-propionylamino]-nicotinic acid



A solution of 3-cyclopentyl-2-(3,4-dichloro-phenyl)-N-(5-carboxymethylpyridin)-2-yl-propionamide (prepared in Example 38(B)(b), 50 mg, 0.12 mmol) in ethanol (10 mL) at 10 25°C was treated with a solution of potassium hydroxide (20 mg, 0.36 mmol) in water (2 mL). The reaction was stirred at 25°C for 2 h. At this time, the reaction was diluted with water (5 mL). The ethanol was removed *in vacuo*. The aqueous layer was then acidified to pH = 2 with a 1N aqueous hydrochloric acid solution. This solution was extracted with methylene chloride (3 x 10 mL). The organic layers were dried over sodium sulfate, 15 filtered and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 80/20 hexanes/ethyl acetate with acetic acid) afforded 6-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionylamino]-nicotinic acid (34 mg, 71%) as white foam: EI-HRMS  $m/e$  calcd for  $C_{20}H_{20}Cl_2N_2O_3$  ( $M^+$ ) 406.0851, found 406.0852.

A solution of 6-[3-cyclopentyl-2-(4-methanesulfonyl-phenyl)-propionylamino]-nicotinic acid methyl ester (prepared in Example 53(B)(a), 100 mg, 0.23 mmol) in tetrahydrofuran (500  $\mu$ L) was treated with a 0.8M aqueous lithium hydroxide solution (300  $\mu$ L, 0.23 mmol). The solution was stirred at 25°C for 4 h. The reaction mixture was then directly  
5 purified by column chromatography. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/3 methanol/ethyl acetate) afforded 6-[3-cyclopentyl-2-(4-methanesulfonyl-phenyl)-propionylamino]-nicotinic acid (65 mg, 70%) as a white solid: mp 191-193°C; FAB-HRMS  $m/e$  calcd for  $C_{21}H_{24}N_2O_5S$  ( $M+H$ )<sup>+</sup> 417.1484, found 417.1484.

10

**Example 49****3-Cyclopentyl-2-(3,4-dichloro-phenyl)-N-(5-hydroxymethyl-pyridin-2-yl)-propionamide**

A solution of 3-cyclopentyl-2-(3,4-dichloro-phenyl)-N-(5-carboxymethylpyridin)-2-yl-  
15 propionamide (prepared in Example 38(B)(b), 398 mg, 0.95 mmol) in diethyl ether (30 mL) cooled to 0°C was treated with lithium aluminum hydride (54 mg, 1.4 mmol). This slurry was allowed to slowly warm to 25°C. The reaction was stirred at 25°C for 16 h. At this time, the reaction was quenched with water (10 mL) and extracted with ethyl acetate (3 x 15 mL). The organics were dried over sodium sulfate, filtered, and  
20 concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(3,4-dichloro-phenyl)-N-(5-hydroxymethyl-pyridin-2-yl)-propionamide (131 mg, 35%) as a white foam: EI-HRMS  $m/e$  calcd for  $C_{20}H_{22}Cl_2N_2O_2$  ( $M^+$ ) 392.1058, found 392.1062.

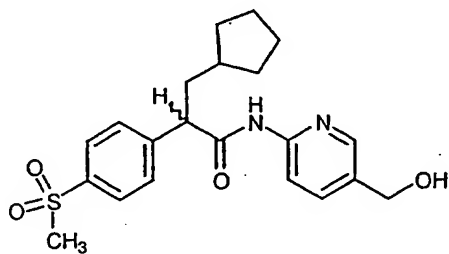
5 treated with a 2.0M solution of oxalyl chloride in methylene chloride (0.35 mL, 0.7 mmol) and a few drops of *N,N*-dimethylformamide. The reaction mixture was stirred at 0°C for 10 min and then at 25°C for 30 min. The reaction mixture was then treated with 5-benzyloxy-pyridin-2-ylamine (281 mg, 1.4 mmol) and *N,N*-diisopropylethylamine (0.26 mL, 1.5 mmol). The reaction mixture was stirred at 25°C for 16 h. At this time, the reaction was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 70/30 hexanes/ethyl acetate) afforded *N*-(5-benzyloxy-pyridin-2-yl)-3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionamide (150 mg, 50.0%) as a yellow solid: mp 47-49°C; EI-HRMS *m/e* calcd for  $C_{26}H_{26}Cl_2N_2O_2$  ( $M^+$ ) 469.1449, found 469.1455.

10

A solution of *N*-(5-benzyloxy-pyridin-2-yl)-3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionamide (145.3 mg, 0.3 mmol) in methanol (5.1 mL) was treated with 10% palladium on activated carbon. The reaction mixture was stirred under hydrogen gas at 25°C for 16 h. The catalyst was then filtered off through a pad of celite (ethyl acetate).  
15 The filtrate was concentrated *in vacuo* to give 3-cyclopentyl-2-(3,4-dichloro-phenyl)-*N*-(5-hydroxy-pyridin-2-yl)-propionamide (92.2 mg, 78.5%) as a tan solid: mp 79-81°C; EI-HRMS *m/e* calcd for  $C_{19}H_{20}Cl_2N_2O_2$  ( $M^+$ ) 378.0896, found 378.0890.

### Example 52

20 **3-Cyclopentyl-*N*-(5-hydroxymethyl-pyridin-2-yl)-2-(4-methanesulfonyl-phenyl)-propionamide**



A solution of 6-[3-cyclopentyl-2-(4-methanesulfonyl-phenyl)-propionylamino]-nicotinic acid methyl ester (prepared in example 53(B)(a), 110 mg, 0.26 mmol) in diethyl ether

purified by flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate) to afford impure 3-cyclopentyl-2-(4-methanesulfonyl-phenyl)-N-(5-methyl-pyridin-2-yl)-propionamide as a red solid. The impure product was further purified by precipitation from 1/1 hexanes/ethyl acetate to afford pure 3-cyclopentyl-2-(4-methanesulfonyl-phenyl)-N-(5-methyl-pyridin-2-yl)-propionamide (80 mg, 31%) as an off-white solid: mp 184-185°C; EI-HRMS m/e calcd for  $C_{21}H_{26}N_2O_3S$  ( $M^+$ ) 386.1664, found 386.1664.

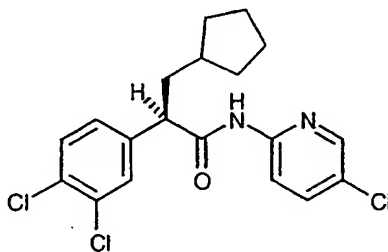
(B) In an analogous manner, there was obtained:

- 10 (a) From 3-cyclopentyl-2-(4-methanesulfonyl-phenyl)propionic acid and 6-aminonicotinic acid methyl ester: 6-[3-Cyclopentyl-2-(4-methanesulfonyl-phenyl)-propionylamino]-nicotinic acid methyl ester as a yellow foam: mp 82-85°C; EI-HRMS m/e calcd for  $C_{22}H_{26}N_2O_5S$  ( $M^+$ ) 430.1562, found 430.1571.

15

#### Example 54

(A) N-(5-Chloro-pyridin-2-yl)-3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionamide



- 20 A solution of 3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionic acid (prepared in Example 38, 5.00 g, 17.4 mmol) in tetrahydrofuran (150 mL) cooled to -78°C was treated with triethylamine (2.77 mL, 19.9 mmol) followed by trimethylacetyl chloride (2.24 mL, 18.2 mmol). The resulting white slurry was stirred at -78°C for 15 min and then at 0°C for 45 min. In a separate flask, a solution of (S)-4-isopropyl-2-oxazolidinone (2.14 g, 16.57

filtered, and concentrated *in vacuo* to afford of 3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionic acid (928 mg, 70%) as a white solid: mp 75.1-78.3°C;  $[\alpha]_{589}^{23} = -50.3^\circ$  ( $c=0.100$ , chloroform); EI-HRMS  $m/e$  calcd for  $C_{14}H_{16}Cl_2O_2$  ( $M^+$ ) 286.0527, found 286.0535.

5

A solution of triphenylphosphine (344 mg, 1.31 mmol) in methylene chloride (10 mL) cooled to 0°C was treated with *N*-bromosuccinimide (263 mg, 1.48 mmol). The reaction solution was stirred at 0°C for 5 min. At this time, 3-cyclopentyl-2-(R)-(3,4-dichloro-phenyl) propionic acid (250 mg, 0.87 mmol) was added. The reaction was allowed to slowly warm to 25°C over 45 min. At this time, 5-chloro-2-aminopyridine (145 mg, 1.13 mmol) and pyridine (0.11 mL, 1.31 mmol) were added to the reaction mixture. The reaction was stirred at 25°C for 20 h. At this time, the reaction was diluted with water (10 mL) and extracted with methylene chloride (3 x 10 mL). The organics were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 90/10 hexanes/ethyl acetate) afforded N-(5-chloro-pyridin-2-yl)3-cyclopentyl-2-(R)-(3,4-dichloro-phenyl)-propionamide (289 mg, 84%) as a white solid: mp 125-128°C;  $[\alpha]_{589}^{23} = -65.6^\circ$  ( $c=0.16$ , chloroform); EI-HRMS  $m/e$  calcd for  $C_{19}H_{19}Cl_3N_2O$  ( $M^+$ ) 396.0563, found 396.0565.

20 (B) In an analogous manner, there were obtained:

(a) From 2-amino pyridine and 3-cyclopentyl-2-(R)-(3,4-dichloro-phenyl) propionic acid : 3-Cyclopentyl-2(R)-(3,4-dichloro-phenyl)-N-pyridin-2-yl-propionamide as a white foam:  $[\alpha]_{589}^{23} = -56.2^\circ$  ( $c=0.153$ , chloroform); EI-HRMS  $m/e$  calcd for  $C_{19}H_{20}Cl_2N_2O$  ( $M^+$ ) 362.0953, found 362.0952.

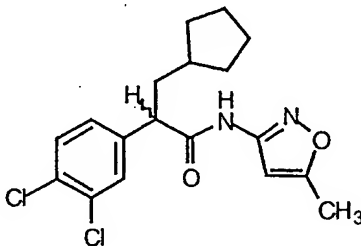
25 (b) From 2-aminothiazole and 3-cyclopentyl-2-(R)-(3,4-dichloro-phenyl) propionic acid: 3-Cyclopentyl-2(R)-(3,4-dichloro-phenyl)-N-thiazol-2-yl-propionamide as a white solid: mp 133.4-136.5°C;  $[\alpha]_{589}^{23} = -66.0^\circ$  ( $c=0.106$ , chloroform); EI-HRMS  $m/e$  calcd for  $C_{17}H_{18}Cl_2N_2OS$  ( $M^+$ ) 368.0517, found 368.0519.



N-(1H-imidazol-2-yl)-propionamide (81.4 mg, 33%) as a white solid: mp 58-60°C; EI-HRMS m/e calcd for  $C_{17}H_{19}Cl_2N_3O$  ( $M^+$ ) 351.0905, found 351.0901.

### Example 56

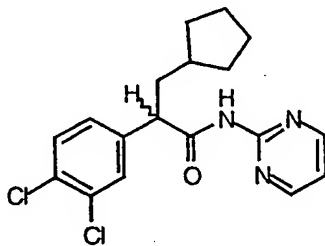
#### 5      3-Cyclopentyl-2-(3,4-dichlorophenyl)-N-(5-methyl-isoxazol-3-yl)-propionamide



A solution of 3-cyclopentyl-2-(3,4-dichlorophenyl)-propionic acid (prepared in Example 38, 70.7 mg, 0.25 mmol) in oxalyl chloride (215  $\mu$ L, 2.46 mmol) was cooled to 0°C and then treated with 1 drop of dry *N,N*-dimethylformamide. The reaction mixture was stirred at 0°C for 30 min and then stirred at 25°C for 3 h. The reaction mixture was concentrated *in vacuo* to afford a yellow oil. This yellow oil was dissolved in a small amount of methylene chloride and then slowly added to a solution of 3-amino-5-methylisoxazole (48.3 mg, 0.49 mmol) and triethylamine (68 mL, 0.49 mmol) in methylene chloride (1.2 mL). The resulting reaction mixture was stirred at 25°C for 14 h. The reaction mixture was concentrated *in vacuo* to remove methylene chloride. The resulting residue was diluted with ethyl acetate (100 mL) and then washed with a 10% aqueous hydrochloric acid solution. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 3/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(3,4-dichlorophenyl)-N-(5-methyl-isoxazol-3-yl)-propionamide (78.3 mg, 87%) as a yellow glass: mp 84-86°C; FAB-HRMS m/e calcd for  $C_{18}H_{20}Cl_2N_2O_2$  ( $M+H$ )<sup>+</sup> 367.0981, found 367.0982.

A solution of 3-cyclopentyl-2-(3,4-dichlorophenyl)-propionic acid (prepared in Example 38, 625.2 mg, 2.18 mmol), *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (908.3 mg, 2.39 mmol), *N,N*-diisopropylethylamine (1.1 mL, 6.53 mmol), and 3-aminopyridazine (310.6 mg, 3.27 mmol) in dry *N,N*-dimethylformamide (11 mL) was stirred at 25°C under nitrogen for 72 h. The reaction mixture was concentrated *in vacuo* to remove *N,N*-dimethylformamide. The resulting residue was diluted with ethyl acetate (200 mL). The organic layer was washed with a 10% aqueous hydrochloric acid solution and washed with a saturated aqueous sodium chloride solution. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(3,4-dichlorophenyl)-*N*-pyridazin-3-yl-propionamide (493.8 mg, 62%) as a white foam: mp 70-71°C; EI-HRMS *m/e* calcd for C<sub>18</sub>H<sub>19</sub>Cl<sub>2</sub>N<sub>3</sub>O (*M*<sup>+</sup>) 363.0905, found 363.0908.

15

**Example 59****3-Cyclopentyl-2-(3,4-dichlorophenyl)-*N*-pyrimidin-2-yl-propionamide**

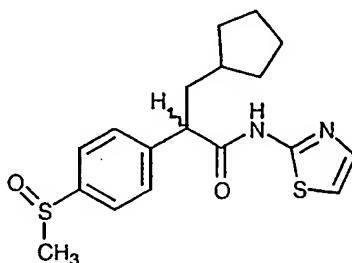
20

A solution of 3-cyclopentyl-2-(3,4-dichlorophenyl)-propionic acid (prepared in Example 38, 100 mg, 0.35 mmol) in methylene chloride (1 mL) was treated with 2 drops of dry *N,N*-dimethylformamide. The reaction mixture was cooled to 0°C and then treated dropwise with oxalyl chloride (34 mL, 0.39 mmol). The reaction mixture was stirred at 0°C for 10 min and then stirred at 25°C for 2 h. The reaction mixture was concentrated *in vacuo*. The resulting residue was dissolved in a small amount of methylene chloride and was slowly added to a cooled (0°C) solution of 2-aminopyrimidine (67 mg, 0.70 mmol) in

phenyl)-N-pyrimidin-4-yl-propionamide (147 mg, 60%) as a white solid: mp 166.5-169.3°C; EI-HRMS m/e calcd for  $C_{18}H_{19}Cl_2N_3O$  ( $M^+$ ) 363.0905, found 363.0909.

### Example 61

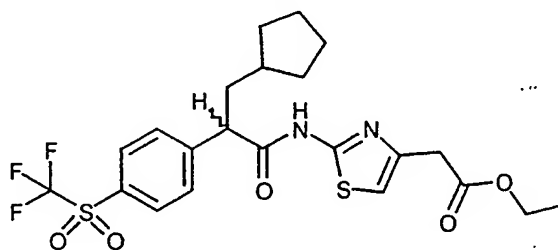
#### 5      3-Cyclopentyl-2-(4-methanesulfinyl-phenyl)-N-thiazol-2-yl-propionamide



A solution of diisopropylamine (3.2 mL, 23.16 mmol) in dry tetrahydrofuran (10.3 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (3.4 mL) was cooled to -78°C under nitrogen and then treated with a 10M solution of *n*-butyllithium in hexanes (2.3 mL, 23.16 mmol). The resulting reaction mixture was stirred at -78°C for 30 min and then treated dropwise with a solution of 4-(methylthio)phenylacetic acid (2.01 g, 11.03 mmol) in dry tetrahydrofuran (10.3 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (3.4 mL). The reaction mixture was allowed to stir at -78°C for 1 h, at which time, a solution of iodomethylcyclopentane (2.55 g, 12.13 mmol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was stirred at -78°C for 30 min and then allowed to warm to 25°C where it was stirred for 24 h. The reaction mixture was quenched with water and then concentrated *in vacuo* to remove tetrahydrofuran. The remaining aqueous phase was acidified to pH = 2 with a 10% aqueous hydrochloric acid solution and then extracted with ethyl acetate (1 x 200 mL). The organic layer was washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-methylsulfonyl-phenyl)propionic acid (1.01 g, 35%) as a cream solid: mp 91-93°C; EI-HRMS m/e calcd for  $C_{15}H_{20}O_2S$  ( $M^+$ ) 264.1184, found 264.1177.

## Example 62

{2-[3-Cyclopentyl-2-(4-trifluoromethanesulfonyl-phenyl)-propionylamino]-thiazol-4-yl}-acetic acid ethyl ester



5

A solution of diisopropylamine (2.4 mL, 16.80 mmol) in dry tetrahydrofuran (7.5 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (2.5 mL) was cooled to -78°C under nitrogen and then treated with a 2.5M solution of *n*-butyllithium in hexanes (6.7 mL, 16.80 mmol). The resulting reaction mixture was stirred at -78°C for 30 min and then treated dropwise with a solution of 4-(trifluoromethylthio)phenylacetic acid (1.89 g, 8.00 mmol) in dry tetrahydrofuran (7.5 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (2.5 mL). The reaction mixture was allowed to stir at -78°C for 55 min, at which time, a solution of iodomethylcyclopentane (1.85 g, 8.80 mmol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was allowed to warm to 25°C where it was stirred for 41 h. The reaction mixture was quenched with water and then concentrated *in vacuo* to remove tetrahydrofuran. The remaining aqueous phase was acidified to pH = 2 with a 10% aqueous hydrochloric acid solution and then extracted with ethyl acetate (1 x 300 mL). The organic layer was washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-trifluoromethylsulfonylphenyl)propionic acid (1.47 g, 58%) as a cream solid: mp 69-71°C; EI-HRMS *m/e* calcd for C<sub>15</sub>H<sub>17</sub>F<sub>3</sub>O<sub>2</sub>S (M<sup>+</sup>) 318.0901, found 318.0912.

10

15

20

A solution of 3-cyclopentyl-2-(4-trifluoromethanesulfonyl-phenyl)propionic acid methyl ester (708.2 mg, 1.94 mmol) in tetrahydrofuran (2.4 mL) was treated with a 0.8M aqueous lithium hydroxide solution (3.6 mL, 2.92 mmol). The reaction mixture was stirred at 25°C for 23 h and then concentrated *in vacuo* to remove tetrahydrofuran. The remaining aqueous layer was acidified to pH = 2 with a 10% aqueous hydrochloric acid solution and then extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a cream solid. This solid was purified by triturating with diethyl ether/petroleum ether to provide pure 3-cyclopentyl-2-(4-trifluoromethanesulfonyl-phenyl)propionic acid (527.0 mg, 77%) as a white solid: mp 143-145°C; EI-HRMS *m/e* calcd for C<sub>15</sub>H<sub>17</sub>F<sub>3</sub>O<sub>4</sub>S (M<sup>+</sup>) 350.0800, found 350.0816.

A solution of triphenylphosphine (97 mg, 0.371 mmol) in methylene chloride (1.5 mL) was cooled to 0°C and then slowly treated with *N*-bromosuccinimide (66 mg, 0.371 mmol). The reaction mixture was stirred at 0°C for 20 min and then treated with 3-cyclopentyl-2-(4-trifluoromethanesulfonyl-phenyl)propionic acid (100 mg, 0.285 mmol). The resulting reaction mixture was stirred at 0°C for 10 min, allowed to warm to 25°C, and then treated with ethyl 2-amino-4-thiazoleacetate (123 mg, 0.657 mmol). The resulting reaction mixture was stirred at 25°C for 3 d. The reaction mixture was then concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 3/1 hexanes/ethyl acetate) afforded {2-[3-cyclopentyl-2-(4-trifluoromethanesulfonyl-phenyl)propionyl-amino]-thiazol-4-yl}-acetic acid ethyl ester (107 mg, 72%) as a yellow foam: mp 48-51°C; EI-HRMS *m/e* calcd for C<sub>22</sub>H<sub>25</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub>S<sub>2</sub> (M<sup>+</sup>) 518.1157, found 518.1157.

A solution of 3-cyclopentyl-2-(4-trifluoromethylsulfanyl-phenyl)propionic acid (1.33 g, 4.18 mmol) in methanol (10 mL) was treated slowly with 4 drops of concentrated sulfuric acid. The resulting reaction mixture was heated under reflux for 36 h. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo* to remove methanol.

5 The residue was diluted with ethyl acetate (200 mL). The organic phase was washed with a saturated aqueous sodium bicarbonate solution (1 x 100 mL), washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 97/3 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-trifluoromethylsulfanyl-phenyl)propionic acid methyl ester (1.37 g, 99%) as a light yellow oil: EI-HRMS m/e

10 calcd for  $C_{16}H_{19}F_3O_2S$  ( $M^+$ ) 332.1058, found 332.1052.

A solution of 3-cyclopentyl-2-(4-trifluoromethylsulfanyl-phenyl)propionic acid methyl ester (1.14 g, 3.43 mmol) in methylene chloride (8.6 mL) was treated with 3-chloroperoxybenzoic acid (80-85% grade, 2.00 g based on 80%, 9.26 mmol). The

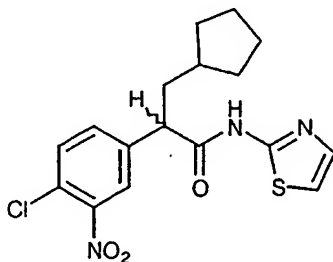
15 reaction mixture was stirred at 25°C for 17 h, at which time, thin layer chromatography showed the presence of two new lower  $R_f$  products. An additional 2.00 g of 3-chloroperoxybenzoic acid was added to the reaction mixture to drive the conversion of the sulfoxide to the sulfone, and the resulting reaction mixture was stirred at 25°C for 3 d.

20 The reaction mixture was concentrated *in vacuo* to remove methylene chloride. The resulting residue was diluted with ethyl acetate (300 mL). The organic phase was washed with a saturated aqueous sodium bicarbonate solution (3 x 100 mL), washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230

25 mesh, 19/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-trifluoromethanesulfonyl-phenyl)propionic acid methyl ester (1.19 g, 95%) as a light yellow oil: EI-HRMS m/e calcd for  $C_{16}H_{19}F_3O_4S$  ( $M^+$ ) 364.0956, found 364.0965.

## Example 64

## 2-(4-Chloro-3-nitro-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide



A solution of 4-chloro-3-nitrophenylacetamide (2.00 g, 9.32 mmol) in methanol (40 mL) was treated with Amberlyst® 15 ion exchange resin (15.00 g). The resulting reaction mixture was heated under reflux for 64 h. The reaction mixture was allowed to cool to 25°C and then filtered to remove the Amberlyst® 15 ion exchange resin. The filtrate was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 3/1 hexanes/ethyl acetate) afforded 4-chloro-3-nitrophenylacetic acid methyl ester (1.91 g, 89%) as a yellow oil: EI-HRMS *m/e* calcd for C<sub>9</sub>H<sub>8</sub>ClNO<sub>4</sub> (M<sup>+</sup>) 229.0142, found 229.0146.

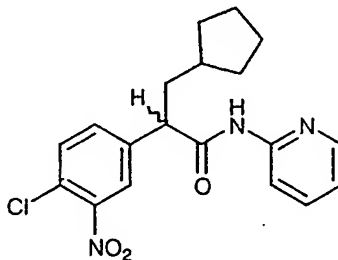
A solution of diisopropylamine (3.35 mL, 23.9 mmol) in dry tetrahydrofuran (45 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (15 mL) was cooled to -78°C and then treated dropwise with a 2.5M solution of *n*-butyllithium in hexanes (9.56 mL, 23.9 mmol) over a 10 min period. The pale yellow reaction mixture was stirred at -78°C for 20 min and then slowly treated with a solution of 4-chloro-3-nitrophenylacetic acid methyl ester (5.00 g, 21.8 mmol) in a small amount of tetrahydrofuran over a 15 min period. The reaction mixture turned deep purple (almost black) in color. The reaction mixture was then stirred at -78°C for 1 h, at which time, a solution of iodomethylcyclopentane (4.58 g, 21.8 mol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was then stirred at -78°C and then allowed to warm to 25°C, where it was stirred for 48 h. The reaction mixture was quenched with a saturated aqueous ammonium chloride solution (50 mL), and the resulting reaction

400 mesh, 3/1 hexanes/ethyl acetate). The pure 2-(4-chloro-3-nitro-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide (93 mg, 73%) was obtained as a pale yellow foam: mp 68-72°C (foam to gel); EI-HRMS *m/e* calcd for C<sub>17</sub>H<sub>18</sub>ClN<sub>3</sub>O<sub>3</sub>S (M<sup>+</sup>) 379.0757, found 379.0760.

5

### Example 65

#### 2-(4-Chloro-3-nitro-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide



10 A solution of 4-chloro-3-nitrophenylacetamide (2.00 g, 9.32 mmol) in methanol (40 mL) was treated with Amberlyst® 15 ion exchange resin (15.00 g). The resulting reaction mixture was heated under reflux for 64 h. The reaction mixture was allowed to cool to 25°C and then filtered to remove the Amberlyst® 15 ion exchange resin. The filtrate was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 3/1 hexanes/ethyl acetate) afforded 4-chloro-3-nitro-phenylacetic acid methyl ester (1.91 g, 15 89%) as a yellow oil: EI-HRMS *m/e* calcd for C<sub>9</sub>H<sub>8</sub>ClNO<sub>4</sub> (M<sup>+</sup>) 229.0142, found 229.0146.

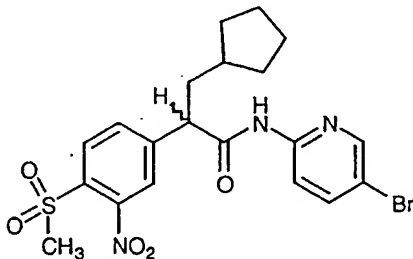
20 A solution of diisopropylamine (3.35 mL, 23.9 mmol) in dry tetrahydrofuran (45 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (15 mL) was cooled to -78°C and then treated dropwise with a 2.5M solution of *n*-butyllithium in hexanes (9.56 mL, 23.9 mmol) over a 10 min period. The pale yellow reaction mixture was stirred at -78°C for 20 min and then slowly treated with a solution of 4-chloro-3-nitrophenylacetic acid methyl ester (5.00 g, 21.8 mmol) in a small amount of tetrahydrofuran over a 15 min



chloro-3-nitro-phenyl)-3-cyclopentyl-propionic acid (100 mg, 0.336 mmol). The resulting reaction mixture was stirred at 0°C for 10 min and then allowed to warm to 25°C, where it was stirred for 20 min. The reaction mixture was then treated with 2-aminopyridine (70 mg, 0.739 mmol). The resulting reaction mixture was stirred at 25°C for 15 h. The crude reaction mixture was treated with a solution of hexanes/ethyl acetate (2 mL, 3:1) and then directly purified by flash chromatography (Merck Silica gel 60, 230-400 mesh, 3/1 hexanes/ethyl acetate). The pure 2-(4-chloro-3-nitro-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide (60 mg, 48%) was obtained as a pale yellow foam: mp 48-52°C (foam to gel); EI-HRMS m/e calcd for C<sub>19</sub>H<sub>20</sub>ClN<sub>3</sub>O<sub>3</sub> (M<sup>+</sup>) 373.1193, found 373.1185.

#### Example 66

##### N-(5-Bromo-pyridin-2-yl)-3-cyclopentyl-2-(4-methanesulfonyl-3-nitro-phenyl)-propionamide



15

A solution of 4-chloro-3-nitrophenylacetamide (2.00 g, 9.32 mmol) in methanol (40 mL) was treated with Amberlyst® 15 ion exchange resin (15.00 g). The resulting reaction mixture was heated under reflux for 64 h. The reaction mixture was allowed to cool to 25°C and then filtered to remove the Amberlyst® 15 ion exchange resin. The filtrate was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 3/1 hexanes/ethyl acetate) afforded 4-chloro-3-nitrophenylacetic acid methyl ester (1.91 g, 89%) as a yellow oil: EI-HRMS m/e calcd for C<sub>9</sub>H<sub>8</sub>ClNO<sub>4</sub> (M<sup>+</sup>) 229.0142, found 229.0146.

methanesulfonyl-3-nitrophenyl)-propionic acid methyl ester (0.95 g, 84%) as a yellow gel; FAB-HRMS *m/e* calcd for  $C_{16}H_{21}NO_6S$  (M+H)<sup>+</sup> 356.1169, found 356.1175.

5 A solution of 3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-propionic acid methyl ester (865 mg, 2.43 mmol) in tetrahydrofuran (6 mL) was treated with a 0.8M aqueous lithium hydroxide solution (4.6 mL, 3.65 mmol). The reaction mixture was stirred at 25°C for 3 h. The reaction mixture was concentrated *in vacuo* to remove tetrahydrofuran. The resulting aqueous residue was diluted with water (25 mL) and then treated with a 1N aqueous hydrochloric acid solution (10 mL). The resulting aqueous layer was then  
10 extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/4 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-propionic acid (723 mg, 87%) as a white foam. Analytical data indicated the presence of a small impurity; however, the 3-cyclopentyl-2-  
15 (4-methanesulfonyl-3-nitrophenyl)-propionic acid was used without further purification in subsequent reactions.

A solution of triphenylphosphine (212 mg, 0.81 mmol) in methylene chloride (3 mL) was cooled to 0°C and then slowly treated with *N*-bromosuccinimide (144 mg, 0.81 mmol).  
20 The reaction mixture was stirred at 0°C for 10 min and then treated with 3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-propionic acid (250 mg, 0.73 mmol). The resulting reaction mixture was stirred at 0°C for 5 min and then allowed to warm to 25°C, where it was stirred for 30 min. The reaction mixture was then treated with 2-amino-5-bromopyridine (279 mg, 1.61 mmol). The resulting reaction mixture was stirred at 25°C  
25 for 15 h. The crude reaction mixture was directly purified by flash chromatography, (Merck Silica gel 60, 230-400 mesh, 3/1 hexanes/ethyl acetate), to afford *N*-(5-bromopyridin-2-yl)-3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-propionamide (121 mg, 33%) as a white foam: mp 80-83°C (foam to gel); FAB-HRMS *m/e* calcd for  $C_{20}H_{22}BrN_3O_5S$  (M+H)<sup>+</sup> 496.0542, found 496.0543.

warm to 25°C, where it was stirred for 48 h. The reaction mixture was quenched with a saturated aqueous ammonium chloride solution (50 mL), and the resulting reaction mixture was concentrated *in vacuo* to remove tetrahydrofuran. The remaining residue was diluted with ethyl acetate (150 mL) and water (50 mL). The organic phase was washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 4/1 hexanes/ethyl acetate) afforded 2-(4-chloro-3-nitrophenyl)-3-cyclopentyl-propionic acid methyl ester (2.17 g, 32%) as a yellow oil: EI-HRMS *m/e* calcd for  $C_{15}H_{18}ClNO_4$  ( $M^+$ ) 311.0924, found 311.0927.

10

A solution of 2-(4-chloro-3-nitrophenyl)-3-cyclopentyl-propionic acid methyl ester (1.00 g, 3.21 mmol) and sodium methanesulfinate (0.36 g, 3.53 mmol) in dimethyl sulfoxide (3 mL) was heated at 130°C for 5 h. The black reaction mixture was then poured over ice (20 g), resulting in the formation of a brown sticky substance. The resulting mixture was then treated with ethyl acetate (50 mL) and water (50 mL), and the layers were separated. The aqueous layer was further extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-propionic acid methyl ester (0.95 g, 84%) as a yellow gel: FAB-HRMS *m/e* calcd for  $C_{16}H_{21}NO_6S$  ( $M+H$ )<sup>+</sup> 356.1169, found 356.1175.

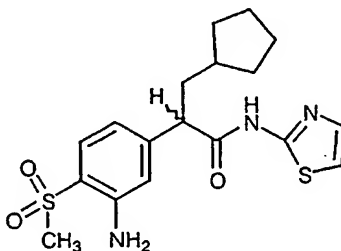
A solution of 3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-propionic acid methyl ester (865 mg, 2.43 mmol) in tetrahydrofuran (6 mL) was treated with a 0.8M aqueous lithium hydroxide solution (4.6 mL, 3.65 mmol). The reaction mixture was stirred at 25°C for 3 h. The reaction mixture was concentrated *in vacuo* to remove tetrahydrofuran. The resulting aqueous residue was diluted with water (25 mL) and then treated with a 1N aqueous hydrochloric acid solution (10 mL). The resulting aqueous layer was then extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried over

25

a white solid: mp 124-126°C; EI-HRMS m/e calcd for  $C_{18}H_{23}N_3O_4S_2$  ( $M^+$ ) 409.1130, found 409.1131.

### Example 68

#### 5 2-(3-Amino-4-methanesulfonyl-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide



A solution of 4-chloro-3-nitrophenylacetamide (2.00 g, 9.32 mmol) in methanol (40 mL) was treated with Amberlyst® 15 ion exchange resin (15.00 g). The resulting reaction mixture was heated under reflux for 64 h. The reaction mixture was allowed to cool to 25°C and then filtered to remove the Amberlyst® 15 ion exchange resin. The filtrate was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 3/1 hexanes/ethyl acetate) afforded 4-chloro-3-nitrophenylacetic acid methyl ester (1.91 g, 89%) as a yellow oil: EI-HRMS m/e calcd for  $C_9H_8ClNO_4$  ( $M^+$ ) 229.0142, found 229.0146.

15

A solution of diisopropylamine (3.35 mL, 23.9 mmol) in dry tetrahydrofuran (45 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (15 mL) was cooled to -78°C and then treated dropwise with a 2.5M solution of *n*-butyllithium in hexanes (9.56 mL, 23.9 mmol) over a 10 min period. The pale yellow reaction mixture was stirred at -78°C for 20 min and then slowly treated with a solution of 4-chloro-3-nitrophenylacetic acid methyl ester (5.00 g, 21.8 mmol) in a small amount of tetrahydrofuran over a 15 min period. The reaction mixture turned deep purple (almost black) in color. The reaction mixture was then stirred at -78°C for 1 h, at which time, a solution of iodomethylcyclopentane (4.58 g, 21.8 mol) in a small amount of dry tetrahydrofuran was

extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/4 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-propionic acid (723 mg, 87%) as a white foam.

5 Analytical data indicated the presence of a small impurity; however, the 3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-propionic acid was used without further purification in subsequent reactions.

A solution of triphenylphosphine (138 mg, 0.53 mmol) in methylene chloride (2 mL) was cooled to 0°C and then slowly treated with *N*-bromosuccinimide (94 mg, 0.53 mmol).

10 The reaction mixture was stirred at 0°C for 10 min and then treated with 3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-propionic acid (150 mg, 0.44 mmol). The resulting reaction mixture was stirred at 0°C for 5 min and then allowed to warm to 25°C, where it was stirred for 25 min. The reaction mixture was then treated with 2-aminothiazole (97

15 mg, 0.97 mmol). The resulting reaction mixture was stirred at 25°C for 15 h. The crude reaction mixture was directly purified by flash chromatography, (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate), to afford 3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-*N*-thiazol-2-yl-propionamide (96 mg, 52%) as a pale yellow solid: mp 121-124°C; FAB-HRMS *m/e* calcd for C<sub>18</sub>H<sub>21</sub>N<sub>3</sub>O<sub>5</sub>S<sub>2</sub> (M+H)<sup>+</sup> 424.1001, found

20 424.1000.

A solution of 3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-*N*-thiazol-2-yl-propionamide (100 mg, 0.236 mmol) in methanol (2 mL) was treated with a solution of ammonium chloride (27 mg, 0.500 mmol) in water (200 µL). The reaction mixture was

25 then treated with zinc dust (151 mg, 2.31 mmol). The reaction mixture was heated under reflux for 2 h. The reaction mixture was allowed to cool to 25°C and then filtered through a pad of celite. The celite pad was washed well with methanol. The filtrate was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate) afforded 2-(3-amino-4-methanesulfonyl-phenyl)-3-cyclopentyl-*N*-

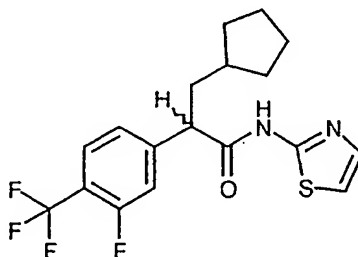
(2.50 g, 10.0 mmol) in a small amount of tetrahydrofuran. The reaction mixture was allowed to stir at -78°C for 1 h, at which time, a solution of iodomethylcyclopentane (2.10 g, 10.0 mmol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was allowed to warm to 25°C where it was stirred for 15 h. The reaction mixture was quenched with water (50 mL) and then partitioned between water (75 mL) and ethyl acetate (75 mL). The layers were shaken and separated. The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 8/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(3-trifluoromethylsulfanyl-phenyl)-propionic acid methyl ester (2.95 g, 89%) as a colorless oil: EI-HRMS *m/e* calcd for C<sub>16</sub>H<sub>19</sub>F<sub>3</sub>O<sub>2</sub>S (M<sup>+</sup>) 332.1058, found 332.1047.

A solution of 3-cyclopentyl-2-(3-trifluoromethylsulfanyl-phenyl)-propionic acid methyl ester (2.75 g, 8.27 mmol) in methylene chloride (30 mL) was treated with 3-chloroperoxybenzoic acid (80-85% grade, 4.28 g based on 80%, 20.67 mmol). The reaction mixture was stirred at 25°C for 6 h, at which time, thin layer chromatography showed the presence of two new lower R<sub>f</sub> products. An additional 4.00 g of 3-chloroperoxybenzoic acid was added to the reaction mixture to drive the conversion of the sulfoxide to the sulfone, and the resulting reaction mixture was stirred at 40°C for 3 d. The reaction mixture was allowed to cool to 25°C and then partitioned between water (100 mL) and methylene chloride (100 mL). The layers were shaken and separated. The organic phase was washed twice with a saturated aqueous sodium bicarbonate solution, washed with water, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/methylene chloride) afforded 3-cyclopentyl-2-(3-trifluoromethanesulfonyl-phenyl)-propionic acid methyl ester (2.07 g, 69%) as a colorless oil: EI-HRMS *m/e* calcd for C<sub>16</sub>H<sub>19</sub>F<sub>3</sub>O<sub>4</sub>S (M<sup>+</sup>) 364.0956, found 364.0947.

A solution of 3-cyclopentyl-2-(3-trifluoromethanesulfonyl-phenyl)-propionic acid methyl ester (1.28 g, 3.52 mmol) in tetrahydrofuran (12 mL) was treated with a 0.8M aqueous

## Example 70

## 3-Cyclopentyl-2-(3-fluoro-4-trifluoromethyl-phenyl)-N-thiazol-2-yl-propionamide

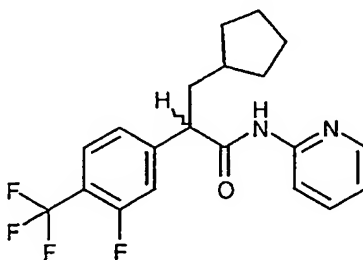


A solution of 3-fluoro-4-(trifluoromethyl)phenylacetic acid (2.50 g, 11.25 mmol) in  
5 methanol (25 mL) was treated slowly with 4 drops of concentrated sulfuric acid. The  
resulting reaction mixture was heated under reflux for 15 h. The reaction mixture was  
allowed to cool to 25°C and then concentrated *in vacuo* to remove methanol. Flash  
chromatography (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate) afforded  
(3-fluoro-4-trifluoromethyl-phenyl)-acetic acid methyl ester (2.58 g, 97%) as a colorless  
10 oil: EI-HRMS *m/e* calcd for C<sub>10</sub>H<sub>8</sub>F<sub>4</sub>O<sub>2</sub> (M<sup>+</sup>) 236.0460, found 236.0457.

A solution of diisopropylamine (1.5 mL, 10.67 mmol) in dry tetrahydrofuran (24 mL) and  
1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (8 mL) was cooled to -78°C under  
nitrogen and then treated with a 2.5M solution of *n*-butyllithium in hexanes (4.3 mL,  
15 10.67 mmol). The resulting reaction mixture was stirred at -78°C for 45 min and then  
treated dropwise with a solution of (3-fluoro-4-trifluoromethyl-phenyl)-acetic acid methyl  
ester (2.40 g, 10.16 mmol) in a small amount of tetrahydrofuran. The reaction mixture  
was allowed to stir at -78°C for 1 h, at which time, a solution of iodomethylcyclopentane  
(2.24 g, 10.67 mmol) in a small amount of dry tetrahydrofuran was added dropwise. The  
20 reaction mixture was allowed to warm to 25°C where it was stirred for 15 h. The reaction  
mixture was quenched with a saturated aqueous ammonium chloride solution (10 mL)  
and then partitioned between water (75 mL) and ethyl acetate (75 mL). The layers were  
shaken and separated. The aqueous layer was further extracted with ethyl acetate (1 x 75  
mL). The combined organic layers were washed with a saturated aqueous sodium

## Example 71

## 3-Cyclopentyl-2-(3-fluoro-4-trifluoromethyl-phenyl)-N-pyridin-2-yl-propionamide



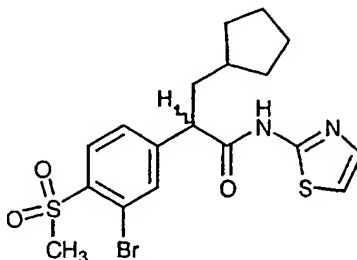
A solution of 3-fluoro-4-(trifluoromethyl)phenylacetic acid (2.50 g, 11.25 mmol) in  
5 methanol (25 mL) was treated slowly with 4 drops of concentrated sulfuric acid. The  
resulting reaction mixture was heated under reflux for 15 h. The reaction mixture was  
allowed to cool to 25°C and then concentrated *in vacuo* to remove methanol. Flash  
chromatography (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate) afforded  
(3-fluoro-4-trifluoromethyl-phenyl)-acetic acid methyl ester (2.58 g, 97%) as a colorless  
10 oil: EI-HRMS *m/e* calcd for C<sub>10</sub>H<sub>8</sub>F<sub>4</sub>O<sub>2</sub> (M<sup>+</sup>) 236.0460, found 236.0457.

A solution of diisopropylamine (1.5 mL, 10.67 mmol) in dry tetrahydrofuran (24 mL) and  
1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (8 mL) was cooled to -78°C under  
nitrogen and then treated with a 2.5M solution of *n*-butyllithium in hexanes (4.3 mL,  
15 10.67 mmol). The resulting reaction mixture was stirred at -78°C for 45 min and then  
treated dropwise with a solution of (3-fluoro-4-trifluoromethyl-phenyl)-acetic acid methyl  
ester (2.40 g, 10.16 mmol) in a small amount of tetrahydrofuran. The reaction mixture  
was allowed to stir at -78°C for 1 h, at which time, a solution of iodomethylcyclopentane  
(2.24 g, 10.67 mmol) in a small amount of dry tetrahydrofuran was added dropwise. The  
20 reaction mixture was allowed to warm to 25°C where it was stirred for 15 h. The reaction  
mixture was quenched with a saturated aqueous ammonium chloride solution (10 mL)  
and then partitioned between water (75 mL) and ethyl acetate (75 mL). The layers were  
shaken and separated. The aqueous layer was further extracted with ethyl acetate (75  
mL). The combined organic layers were washed with a saturated aqueous sodium



## Example 72

## 2-(3-Bromo-4-methanesulfonyl-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide



- 5 A solution of 4-(methylthio)phenylacetic acid (21.21 g, 116.38 mmol) in methanol (291 mL) was treated slowly with concentrated sulfuric acid (3 mL). The resulting reaction mixture was heated under reflux for 3 d. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo* to remove methanol. The resulting residue was diluted with diethyl ether (600 mL). The organic layer was washed with a saturated aqueous sodium bicarbonate solution (3 x 300 mL) and a saturated aqueous sodium chloride solution (1 x 300 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford (4-methylsulfanyl-phenyl)-acetic acid methyl ester (20.95 g, 92%) as a yellow liquid which was used without further purification: EI-HRMS *m/e* calcd for C<sub>10</sub>H<sub>12</sub>O<sub>2</sub>S (M<sup>+</sup>) 196.0558, found 196.0559.

15

- A solution of (4-methylsulfanyl-phenyl)-acetic acid methyl ester (5.11 g, 26.03 mmol) in carbon tetrachloride (130 mL) was slowly treated with bromine (1.74 mL, 33.84 mmol). The reaction mixture was stirred at 25°C for 4 h, at which time, thin layer chromatography still indicated the presence of a substantial amount of starting material.
- 20 The reaction mixture was treated with more bromine (1.74 mL, 33.84 mmol). The reaction mixture was stirred an additional 4 h at 25°C and then quenched with a 10% aqueous sodium bisulfite solution (150 mL). The reaction mixture was concentrated *in vacuo* to remove carbon tetrachloride. The resulting aqueous layer was extracted with ethyl acetate (3 x 150 mL). The combined organic layers were dried over sodium sulfate,

(300 mL). The organic phase was washed with a saturated aqueous sodium bicarbonate solution (3 x 200 mL) and a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/1 hexanes/ethyl acetate) afforded 2-(3-bromo-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (1.09 g, 94%) as a colorless oil: EI-HRMS *m/e* calcd for  $C_{16}H_{19}BrO_4S$  ( $M^+$ ) 388.0344, found 388.0343.

A solution of 2-(3-bromo-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (1.62 g, 4.16 mol) in methanol (10 mL) was treated with a 1N aqueous sodium hydroxide solution (8.7 mL, 8.74 mol). The reaction mixture was stirred at 25°C for 27 h. The reaction mixture was concentrated *in vacuo* to remove methanol. The resulting aqueous residue was acidified to pH = 2 with a 10% aqueous hydrochloric acid solution and then extracted with ethyl acetate (1 x 400 mL). The organic layer was washed with water (1 x 300 mL) and a saturated aqueous sodium chloride solution (1 x 300 mL). The organic layer was then dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford 2-(3-bromo-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid (1.39 g, 89%) as a white solid which was used without further purification: mp 149-150°C; FAB-HRMS *m/e* calcd for  $C_{15}H_{19}BrO_4S$  ( $M+H$ )<sup>+</sup> 375.0266, found 375.0274.

20

A solution of triphenylphosphine (168 mg, 0.64 mmol) in methylene chloride (3 mL) was cooled to 0°C and then slowly treated with *N*-bromosuccinimide (114 mg, 0.64 mmol). The reaction mixture was stirred at 0°C for 10 min and then treated with 2-(3-bromo-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid (200 mg, 0.53 mmol). The resulting reaction mixture was stirred at 0°C for 5 min and then allowed to warm to 25°C where it was stirred for 25 min. The reaction mixture was then treated with 2-aminothiazole (117 mg, 1.17 mmol). The resulting reaction mixture was stirred at 25°C for 15 h. The crude reaction mixture was then directly purified by flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate) to afford 2-(3-bromo-4-

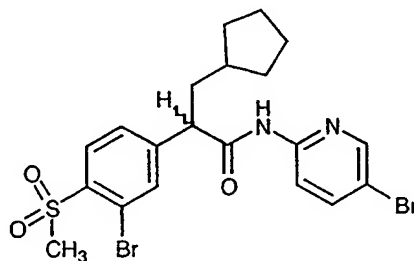
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reaction mixture was stirred an additional 4 h at 25°C and then quenched with a 10% aqueous sodium bisulfite solution (150 mL). The reaction mixture was concentrated *in vacuo* to remove carbon tetrachloride. The resulting aqueous layer was extracted with ethyl acetate (3 x 150 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 9/1 hexanes/ethyl acetate) afforded (3-bromo-4-methylsulfanyl-phenyl)-acetic acid methyl ester (6.10 g, 85%) as a light yellow oil: EI-HRMS *m/e* calcd for C<sub>10</sub>H<sub>11</sub>BrO<sub>2</sub>S (M<sup>+</sup>) 273.9663, found 273.9661.

10 A solution of diisopropylamine (3.4 mL, 24.38 mmol) in dry tetrahydrofuran (21 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (7 mL) was cooled to -78°C under nitrogen and then treated with a 2.5M solution of *n*-butyllithium in hexanes (9.8 mL, 24.38 mmol). The resulting reaction mixture was stirred at -78°C for 30 min and then treated dropwise with a solution of (3-bromo-4-methylsulfanyl-phenyl)-acetic acid methyl ester (6.10 g, 22.17 mmol) in dry tetrahydrofuran (21 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (7 mL). The resulting reaction mixture was allowed to stir at -78°C for 1 h, at which time, a solution of iodomethylcyclopentane (5.59 g, 26.60 mmol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was allowed to warm to 25°C where it was stirred for 15 h. The reaction mixture was quenched with water (300 mL) and then concentrated *in vacuo* to remove tetrahydrofuran. The remaining aqueous phase was extracted with ethyl acetate (3 x 150 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (1 x 200 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 19/1 hexanes/ethyl acetate) afforded 2-(3-bromo-4-methylsulfanyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (4.52 g, 57%) as a light yellow oil: EI-HRMS *m/e* calcd for C<sub>16</sub>H<sub>21</sub>BrO<sub>2</sub>S (M<sup>+</sup>) 356.0446, found 356.0435.

resulting reaction mixture was stirred at 0°C for 5 min and then allowed to warm to 25°C where it was stirred for 25 min. The reaction mixture was then treated with 2-aminopyridine (110 mg, 1.17 mmol). The resulting reaction mixture was stirred at 25°C for 15 h. The crude reaction mixture was then directly purified by flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate) to afford 2-(3-bromo-4-methanesulfonyl-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide (175 mg, 73%) as a white foam: mp 99-101°C; FAB-HRMS m/e calcd for C<sub>20</sub>H<sub>23</sub>BrN<sub>2</sub>O<sub>3</sub>S (M+H)<sup>+</sup> 451.0692, found 451.0689.

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**Example 74****2-(3-Bromo-4-methanesulfonyl-phenyl)-N-(5-bromo-pyridin-2-yl)-3-cyclopentyl-propionamide**

A solution of 4-(methylthio)phenylacetic acid (21.21 g, 116.38 mmol) in methanol (291 mL) was treated slowly with concentrated sulfuric acid (3 mL). The resulting reaction mixture was heated under reflux for 3 d. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo* to remove methanol. The resulting residue was diluted with diethyl ether (600 mL). The organic layer was washed with a saturated aqueous sodium bicarbonate solution (3 x 300 mL) and a saturated aqueous sodium chloride solution (1 x 300 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford (4-methylsulfanyl-phenyl)-acetic acid methyl ester (20.95 g, 92%) as a yellow liquid which was used without further purification: EI-HRMS m/e calcd for C<sub>10</sub>H<sub>12</sub>O<sub>2</sub>S (M<sup>+</sup>) 196.0558, found 196.0559.

methyl ester (4.52 g, 57%) as a light yellow oil: EI-HRMS m/e calcd for  $C_{16}H_{21}BrO_2S$  ( $M^+$ ) 356.0446, found 356.0435.

5 A solution of 2-(3-bromo-4-methylsulfanyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (1.07 g, 2.99 mmol) in methylene chloride (15 mL) was treated with 3-chloroperoxybenzoic acid (57-86% grade, 1.81 g based on 57%, 5.99 mmol). The reaction mixture was stirred at 25°C for 3 h. The reaction mixture was concentrated *in vacuo* to remove methylene chloride. The resulting residue was diluted with diethyl ether (300 mL). The organic phase was washed with a saturated aqueous sodium bicarbonate  
10 solution (3 x 200 mL) and a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/1 hexanes/ethyl acetate) afforded 2-(3-bromo-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (1.09 g, 94%) as a colorless oil: EI-HRMS m/e calcd for  $C_{16}H_{19}BrO_4S$  ( $M^+$ ) 388.0344, found 388.0343.

15

A solution of 2-(3-bromo-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (1.62 g, 4.16 mol) in methanol (10 mL) was treated with a 1N aqueous sodium hydroxide solution (8.7 mL, 8.74 mol). The reaction mixture was stirred at 25°C for 27 h. The reaction mixture was concentrated *in vacuo* to remove methanol. The  
20 resulting aqueous residue was acidified to pH = 2 with a 10% aqueous hydrochloric acid solution and then extracted with ethyl acetate (1 x 400 mL). The organic layer was washed with water (1 x 300 mL) and a saturated aqueous sodium chloride solution (1 x 300 mL). The organic layer was then dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford 2-(3-bromo-4-methanesulfonyl-phenyl)-3-cyclopentyl-  
25 propionic acid (1.39 g, 89%) as a white solid which was used without further purification: mp 149-150°C; FAB-HRMS m/e calcd for  $C_{15}H_{19}BrO_4S$  ( $M+H$ )<sup>+</sup> 375.0266, found 375.0274.

and concentrated *in vacuo* to afford (4-methylsulfanyl-phenyl)-acetic acid methyl ester (20.95 g, 92%) as a yellow liquid which was used without further purification: EI-HRMS m/e calcd for  $C_{10}H_{12}O_2S$  ( $M^+$ ) 196.0558, found 196.0559.

- 5 A solution of (4-methylsulfanyl-phenyl)-acetic acid methyl ester (5.11 g, 26.03 mmol) in carbon tetrachloride (130 mL) was slowly treated with bromine (1.74 mL, 33.84 mmol). The reaction mixture was stirred at 25°C for 4 h, at which time, thin layer chromatography still indicated the presence of a substantial amount of starting material. The reaction mixture was treated with more bromine (1.74 mL, 33.84 mmol). The  
10 reaction mixture was stirred an additional 4 h at 25°C and then quenched with a 10% aqueous sodium bisulfite solution (150 mL). The reaction mixture was concentrated *in vacuo* to remove carbon tetrachloride. The resulting aqueous layer was extracted with ethyl acetate (3 x 150 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230  
15 mesh, 9/1 hexanes/ethyl acetate) afforded (3-bromo-4-methylsulfanyl-phenyl)-acetic acid methyl ester (6.10 g, 85%) as a light yellow oil: EI-HRMS m/e calcd for  $C_{10}H_{11}BrO_2S$  ( $M^+$ ) 273.9663, found 273.9661.

- A solution of diisopropylamine (3.4 mL, 24.38 mmol) in dry tetrahydrofuran (21 mL) and  
20 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (7 mL) was cooled to -78°C under nitrogen and then treated with a 2.5M solution of *n*-butyllithium in hexanes (9.8 mL, 24.38 mmol). The resulting reaction mixture was stirred at -78°C for 30 min and then treated dropwise with a solution of (3-bromo-4-methylsulfanyl-phenyl)-acetic acid methyl ester (6.10 g, 22.17 mmol) in dry tetrahydrofuran (21 mL) and 1,3-dimethyl-3,4,5,6-  
25 tetrahydro-2(1H)-pyrimidinone (7 mL). The resulting reaction mixture was allowed to stir at -78°C for 1 h, at which time, a solution of iodomethylcyclopentane (5.59 g, 26.60 mmol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was allowed to warm to 25°C where it was stirred for 15 h. The reaction mixture was quenched with water (300 mL) and then concentrated *in vacuo* to remove

A solution of 2-(3-cyano-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (4.84 g, 14.4 mol) in tetrahydrofuran (25 mL) was treated with a 0.8M aqueous lithium hydroxide solution (27 mL, 21.6 mmol). The reaction mixture was stirred at 25°C for 2.5 h. The reaction mixture was partitioned between water and ethyl acetate and then acidified to pH = 2 with a 10% aqueous hydrochloric acid solution. The layers were shaken and separated. The resulting organic layer was washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford crude 2-(3-cyano-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid (3.80 g, 82%) as a pale yellow oil that solidified to a pale yellow solid. An analytical sample was obtained by recrystallization from ethyl acetate to afford 2-(3-cyano-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid as a white solid: mp 180-181°C; EI-HRMS m/e calcd for C<sub>16</sub>H<sub>19</sub>NO<sub>4</sub>S (M<sup>+</sup>) 321.1034, found 321.1039.

A solution of triphenylphosphine (98 mg, 0.37 mmol) in methylene chloride (1 mL) was cooled to 0°C and then slowly treated with *N*-bromosuccinimide (67 mg, 0.37 mmol). The reaction mixture was stirred at 0°C for 15 min and then treated with 2-(3-cyano-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid (100 mg, 0.31 mmol). The resulting reaction mixture was stirred at 0°C for 5 min and then allowed to warm to 25°C where it was stirred for 30 min. The reaction mixture was then treated with 2-aminothiazole (68 mg, 0.68 mmol). The resulting reaction mixture was stirred at 25°C for 15 h. The crude reaction mixture was then directly purified by flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate) to afford 2-(3-cyano-4-methanesulfonyl-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide (117 mg, 93%) as a white solid: mp 145-148°C; EI-HRMS m/e calcd for C<sub>19</sub>H<sub>21</sub>N<sub>3</sub>O<sub>3</sub>S<sub>2</sub> (M<sup>+</sup>) 403.1024, found 403.1023.

filtered and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 9/1 hexanes/ethyl acetate) afforded (3-bromo-4-methylsulfanyl-phenyl)-acetic acid methyl ester (6.10 g, 85%) as a light yellow oil: EI-HRMS *m/e* calcd for  $C_{10}H_{11}BrO_2S$  ( $M^+$ ) 273.9663, found 273.9661.

5

A solution of diisopropylamine (3.4 mL, 24.38 mmol) in dry tetrahydrofuran (21 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (7 mL) was cooled to  $-78^{\circ}C$  under nitrogen and then treated with a 2.5M solution of *n*-butyllithium in hexanes (9.8 mL, 24.38 mmol). The reaction mixture was stirred at  $-78^{\circ}C$  for 30 min and then treated  
10 dropwise with a solution of (3-bromo-4-methylsulfanyl-phenyl)-acetic acid methyl ester (6.10 g, 22.17 mmol) in dry tetrahydrofuran (21 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (7 mL). The resulting reaction mixture was allowed to stir at  $-78^{\circ}C$  for 1 h, at which time, a solution of iodomethylcyclopentane (5.59 g, 26.60 mmol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was  
15 allowed to warm to  $25^{\circ}C$  where it was stirred for 15 h. The reaction mixture was quenched with water (300 mL) and then concentrated *in vacuo* to remove tetrahydrofuran. The remaining aqueous phase was extracted with ethyl acetate (3 x 150 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (1 x 200 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash  
20 chromatography (Merck Silica gel 60, 70-230 mesh, 19/1 hexanes/ethyl acetate) afforded 2-(3-bromo-4-methylsulfanyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (4.52 g, 57%) as a light yellow oil: EI-HRMS *m/e* calcd for  $C_{16}H_{21}BrO_2S$  ( $M^+$ ) 356.0446, found 356.0435.

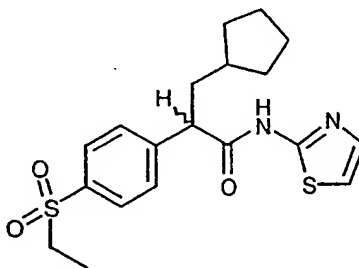
25 A solution of 2-(3-bromo-4-methylsulfanyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (1.07 g, 2.99 mmol) in methylene chloride (15 mL) was treated with 3-chloroperoxybenzoic acid (57-86% grade, 1.81 g based on 57%, 5.99 mmol). The reaction mixture was stirred at  $25^{\circ}C$  for 3 h. The reaction mixture was concentrated *in vacuo* to remove methylene chloride. The resulting residue was diluted with diethyl ether



A solution of triphenylphosphine (98 mg, 0.37 mmol) in methylene chloride (1 mL) was cooled to 0°C and then slowly treated with *N*-bromosuccinimide (67 mg, 0.37 mmol). The reaction mixture was stirred at 0°C for 15 min and then treated with 2-(3-cyano-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid (100 mg, 0.31 mmol). The  
5 resulting reaction mixture was stirred at 0°C for 5 min and then allowed to warm to 25°C where it was stirred for 30 min. The reaction mixture was then treated with 2-aminopyridine (64 mg, 0.68 mmol). The resulting reaction mixture was stirred at 25°C for 15 h. The crude reaction mixture was then directly purified by flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate) to afford 2-(3-cyano-4-methanesulfonyl-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide (94.5 mg, 76%) as  
10 a yellow foam: mp 87-90°C (foam to gel); EI-HRMS *m/e* calcd for C<sub>21</sub>H<sub>23</sub>N<sub>3</sub>O<sub>3</sub>S (M<sup>+</sup>) 397.1460, found 397.1460.

### Example 77

#### 15 3-Cyclopentyl-2-(4-ethanesulfonyl-phenyl)-N-thiazol-2-yl-propionamide



A mixture of aluminum chloride (72.35 g, 0.54 mol) in chloroform (181 mL) was cooled to 0°C and stirred until the solid material dissolved. The reaction mixture was then slowly treated with ethyl oxalyl chloride (61 mL, 0.54 mol), and the resulting reaction  
20 mixture was stirred at 0°C for 30 min. The reaction mixture was then slowly treated with ethyl phenyl sulfide (25.00 g, 0.18 mol). The solution turned to a wine color and slowly became gum-like. The resulting reaction mixture was then stirred at 0°C for 2 h. The reaction mixture was slowly poured into a large amount of ice/water. The resulting aqueous layer was extracted with chloroform (3 x 200 mL). The combined organic layers

m/e calcd for  $C_{18}H_{24}O_2S$  (M+H)<sup>+</sup> integer mass 304, found 305. The isomeric mixture was used without further separation in subsequent reactions.

A solution of 3-cyclopentyl-2-(4-ethylsulfanyl-phenyl)-acrylic acid ethyl ester [5.76 g, 18.92 mmol, (E):(Z) = 1.82:1] in methylene chloride (47 mL) was slowly treated with 3-chloroperoxybenzoic acid (57-86% grade, 11.45 g based on 57%, 37.83 mmol). The reaction mixture was stirred at 25°C for 1 h. The reaction mixture was concentrated *in vacuo* to remove methylene chloride. The resulting residue was diluted with diethyl ether (300 mL). The organic phase was washed with a saturated aqueous sodium bicarbonate solution (3 x 200 mL) and a saturated aqueous sodium chloride solution (1 x 200 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 3/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-ethanesulfonyl-phenyl)-acrylic acid ethyl ester (4.89 g, 77%) as a colorless oil. The product was a 3:1 mixture of (E):(Z) isomers that was used without further purification and characterization.

A solution of 3-cyclopentyl-2-(4-ethanesulfonyl-phenyl)-acrylic acid ethyl ester [4.89 g, 14.53 mmol, (E):(Z) = 3:1] in ethanol (36 mL) was slowly treated with 10% palladium on activated carbon (244.5 mg). The reaction mixture was stirred under a positive pressure of hydrogen gas (balloon) at 25°C and atmospheric pressure for 44 h. The catalyst was then filtered off through a pad of celite, and the celite pad was washed well with ethyl acetate. The filtrate was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-ethanesulfonyl-phenyl)-propionic acid ethyl ester (3.50 g, 71%) as a colorless viscous oil: FAB-LRMS m/e calcd for  $C_{18}H_{26}O_4S$  (M+H)<sup>+</sup> integer mass 338, found 339.

A solution of 3-cyclopentyl-2-(4-ethanesulfonyl-phenyl)-propionic acid ethyl ester (2.50 g, 7.39 mmol) in tetrahydrofuran (30 mL) was treated with a 0.8M aqueous lithium hydroxide solution (11.1 mL, 8.86 mmol). The reaction mixture was stirred at 25°C for

- A mixture of aluminum chloride (72.35 g, 0.54 mol) in chloroform (181 mL) was cooled to 0°C and stirred until the solid material dissolved. The reaction mixture was then slowly treated with ethyl oxalyl chloride (61 mL, 0.54 mol), and the resulting reaction mixture was stirred at 0°C for 30 min. The reaction mixture was then slowly treated with ethyl phenyl sulfide (25.00 g, 0.18 mol). The solution turned to a wine color and slowly became gum-like. The resulting reaction mixture was then stirred at 0°C for 2 h. The reaction mixture was slowly poured into a large amount of ice/water. The resulting aqueous layer was extracted with chloroform (3 x 200 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 9/1 hexanes/ethyl acetate) afforded (4-ethylsulfanyl-phenyl)-oxo-acetic acid ethyl ester (23.64 g, 55%) as a yellow oil. The material was used without further purification and characterization in subsequent reactions.
- 15 A solution of iodomethylcyclopentane (4.60 g, 21.89 mmol) and triphenylphosphine (5.74 g, 21.89 mmol) in acetonitrile (22 mL) was heated under reflux for 2 weeks. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo* to provide an orange solid. The orange solid was triturated with diethyl ether and then filtered. The solid was washed well with diethyl ether until the washings showed the absence of
- 20 iodomethylcyclopentane and triphenylphosphine by thin layer chromatography. The solid was allowed to air dry to afford cyclopentylmethyl triphenylphosphonium iodide (8.92 g, 86%) as a light orange solid: mp 195-198°C; FAB-HRMS *m/e* calcd for C<sub>24</sub>H<sub>26</sub>P (M+H)<sup>+</sup> 345.1772, found 345.1784.
- 25 A suspension of cyclopentylmethyl triphenylphosphonium iodide (24.48 g, 51.82 mmol) in dry tetrahydrofuran (100 mL) was cooled to 0°C and then treated dropwise with a 1.0M solution of sodium bis(trimethylsilyl)amide in tetrahydrofuran (52 mL, 51.82 mmol). The bright orange reaction mixture was stirred at 0°C for 1 h. The reaction mixture was then treated with (4-ethylsulfanyl-phenyl)-oxo-acetic acid ethyl ester (9.50 g, 39.87 mmol).

60, 70-230 mesh, 3/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-ethanesulfonyl-phenyl)-propionic acid ethyl ester (3.50 g, 71%) as a colorless viscous oil: FAB-LRMS  $m/e$  calcd for  $C_{18}H_{26}O_4S$  ( $M+H$ )<sup>+</sup> integer mass 338, found 339.

- 5 A solution of 3-cyclopentyl-2-(4-ethanesulfonyl-phenyl)-propionic acid ethyl ester (2.50 g, 7.39 mmol) in tetrahydrofuran (30 mL) was treated with a 0.8M aqueous lithium hydroxide solution (11.1 mL, 8.86 mmol). The reaction mixture was stirred at 25°C for 23 h. The resulting reaction mixture was partitioned between water (75 mL) and ethyl acetate (75 mL) and then treated with a 1N aqueous hydrochloric acid solution (15 mL).
- 10 The layers were shaken and separated. The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford 3-cyclopentyl-2-(4-ethanesulfonyl-phenyl)-propionic acid (2.20 g, 96%) as a white solid which was used without further purification: mp 137-138°C; FAB-HRMS  $m/e$  calcd for  $C_{16}H_{22}O_4S$  ( $M+H$ )<sup>+</sup> 311.1317, found 311.1321.

15

- A solution of triphenylphosphine (279 mg, 1.06 mmol) in methylene chloride (5 mL) was cooled to 0°C and then slowly treated with *N*-bromosuccinimide (189 mg, 1.06 mmol). The reaction mixture was stirred at 0°C for 20 min and then treated with 3-cyclopentyl-2-(4-ethanesulfonyl-phenyl)-propionic acid (300 mg, 0.97 mmol). The resulting reaction
- 20 mixture was stirred at 0°C for 10 min and then allowed to warm to 25°C where it was stirred for 30 min. The reaction mixture was then treated with 2-aminopyridine (200 mg, 2.13 mmol). The resulting reaction mixture was stirred at 25°C for 15 h. The crude reaction mixture was then directly purified by flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate) to afford 3-cyclopentyl-2-(4-ethanesulfonyl-
- 25 phenyl)-*N*-pyridin-2-yl-propionamide (185 mg, 50%) as a pale orange solid: mp 144-145°C; EI-HRMS  $m/e$  calcd for  $C_{21}H_{26}N_2O_3S$  ( $M^+$ ) 386.1664, found 386.1660.

for 3 h. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo* to remove methanol. The resulting residue was slowly diluted with a saturated aqueous sodium bicarbonate solution (300 mL) and then extracted with ethyl acetate (1 x 300 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford an inseparable, isomeric mixture of (3-fluoro-4-methylsulfanyl-phenyl)-acetic acid methyl ester and (4-fluoro-3-methylsulfanyl-phenyl)-acetic acid methyl ester as a yellow oil (4.65 g, 75%) which was used without further purification and characterization.

10 A solution of the inseparable, isomeric mixture of (3-fluoro-4-methylsulfanyl-phenyl)-acetic acid methyl ester and (4-fluoro-3-methylsulfanyl-phenyl)-acetic acid methyl ester (4.44 g, 20.72 mmol) in methylene chloride (103 mL) was slowly treated with 3-chloroperoxybenzoic acid (57-86% grade, 13.80 g based on 57%, 45.59 mmol). The reaction mixture was stirred at 25°C for 4 h. The reaction mixture was concentrated *in vacuo* to remove methylene chloride. The resulting residue was diluted with ethyl acetate (300 mL). The organic phase was washed with a saturated aqueous sodium bicarbonate solution (1 x 200 mL) and a saturated aqueous sodium chloride solution (1 x 200 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 20/1 methylene chloride/ethyl acetate) afforded an inseparable, isomeric mixture of (3-fluoro-4-methanesulfonyl-phenyl)-acetic acid methyl ester and (4-fluoro-3-methanesulfonyl-phenyl)-acetic acid methyl ester as a colorless liquid (3.31 g, 65%) which was used without further purification and characterization.

25 A solution of the inseparable, isomeric mixture of (3-fluoro-4-methanesulfonyl-phenyl)-acetic acid methyl ester and (4-fluoro-3-methanesulfonyl-phenyl)-acetic acid methyl ester (2.28 g, 9.26 mmol) in dimethyl sulfoxide (23 mL) was treated with sodium thiomethoxide (1.37 g, 18.52 mmol). The reaction mixture was stirred at 25°C for 4 h and then quenched with a 10% aqueous hydrochloric acid solution. The aqueous layer was extracted with chloroform (1 x 400 mL), dried over magnesium sulfate, filtered, and

The remaining residue was further diluted with water (100 mL) and then extracted with ethyl acetate (1 x 250 mL). The organic layer was washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/1 hexanes/ethyl acetate) afforded 2-(3,4-bis-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (1.61 g, 67%) as a yellow oil: EI-HRMS *m/e* calcd for  $C_{17}H_{24}O_6S_2$  ( $M^+$ ) 388.1014, found 388.1014.

A solution of 2-(3,4-bis-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (1.17 g, 3.01 mmol) in tetrahydrofuran (12 mL) was treated with a 0.8M aqueous lithium hydroxide solution (5.6 mL, 4.52 mmol). The reaction mixture was stirred at 25°C for 3 h. The resulting reaction mixture was partitioned between water (75 mL) and ethyl acetate (75 mL) and then treated with a 1N aqueous hydrochloric acid solution (10 mL). The layers were shaken and separated. The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford 2-(3,4-bis-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid (1.10 g, 98%) as a white foam which was used without further purification: mp 64-68°C (foam to gel); FAB-HRMS *m/e* calcd for  $C_{16}H_{22}O_6S_2$  ( $M+H$ )<sup>+</sup> 375.0936, found 375.0932.

A solution of triphenylphosphine (154 mg, 0.59 mmol) in methylene chloride (2 mL) was cooled to 0°C and then slowly treated with *N*-bromosuccinimide (105 mg, 0.59 mmol). The reaction mixture was stirred at 0°C for 10 min and then treated with 2-(3,4-bis-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid (200 mg, 0.53 mmol). The resulting reaction mixture was stirred at 0°C for 5 min and then allowed to warm to 25°C where it was stirred for 30 min. The reaction mixture was then treated with 2-aminothiazole (118 mg, 1.18 mmol). The resulting reaction mixture was stirred at 25°C for 15 h. The crude reaction mixture was then directly purified by flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate) to afford 2-(3,4-bis-methanesulfonyl-phenyl)-3-cyclopentyl-*N*-thiazol-2-yl-propionamide (150 mg, 61%) as a

were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford a yellow oil. This yellow oil was dissolved in methanol (100 mL) and then slowly treated with concentrated sulfuric acid (5 mL). The resulting reaction mixture was heated under reflux for 3 h. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo* to remove methanol. The resulting residue was slowly diluted with a saturated aqueous sodium bicarbonate solution (300 mL) and then extracted with ethyl acetate (1 x 300 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford an inseparable, isomeric mixture of (3-fluoro-4-methylsulfanyl-phenyl)-acetic acid methyl ester and (4-fluoro-3-methylsulfanyl-phenyl)-acetic acid methyl ester as a yellow oil (4.65 g, 75%) which was used without further purification and characterization.

A solution of the inseparable, isomeric mixture of (3-fluoro-4-methylsulfanyl-phenyl)-acetic acid methyl ester and (4-fluoro-3-methylsulfanyl-phenyl)-acetic acid methyl ester (4.44 g, 20.72 mmol) in methylene chloride (103 mL) was slowly treated with 3-chloroperoxybenzoic acid (57-86% grade, 13.80 g based on 57%, 45.59 mmol). The reaction mixture was stirred at 25°C for 4 h. The reaction mixture was concentrated *in vacuo* to remove methylene chloride. The resulting residue was diluted with ethyl acetate (300 mL). The organic phase was washed with a saturated aqueous sodium bicarbonate solution (1 x 200 mL) and a saturated aqueous sodium chloride solution (1 x 200 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 20/1 methylene chloride/ethyl acetate) afforded an inseparable, isomeric mixture of (3-fluoro-4-methanesulfonyl-phenyl)-acetic acid methyl ester and (4-fluoro-3-methanesulfonyl-phenyl)-acetic acid methyl ester as a colorless liquid (3.31 g, 65%) which was used without further purification and characterization.

A solution of the inseparable, isomeric mixture of (3-fluoro-4-methanesulfonyl-phenyl)-acetic acid methyl ester and (4-fluoro-3-methanesulfonyl-phenyl)-acetic acid methyl ester (2.28 g, 9.26 mmol) in dimethyl sulfoxide (23 mL) was treated with sodium

small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was allowed to warm to 25°C where it was stirred for 64 h. The reaction mixture was quenched with water (150 mL) and then concentrated *in vacuo* to remove tetrahydrofuran. The remaining residue was further diluted with water (100 mL) and then extracted with ethyl acetate (1 x 250 mL). The organic layer was washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/1 hexanes/ethyl acetate) afforded 2-(3,4-bis-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (1.61 g, 67%) as a yellow oil: EI-HRMS *m/e* calcd for  $C_{17}H_{24}O_6S_2$  ( $M^+$ ) 388.1014, found 388.1014.

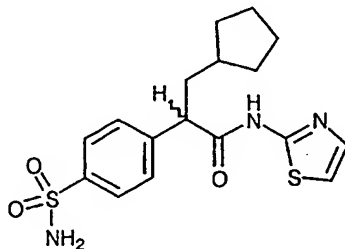
A solution of 2-(3,4-bis-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (1.17 g, 3.01 mmol) in tetrahydrofuran (12 mL) was treated with a 0.8M aqueous lithium hydroxide solution (5.6 mL, 4.52 mmol). The reaction mixture was stirred at 25°C for 3 h. The resulting reaction mixture was partitioned between water (75 mL) and ethyl acetate (75 mL) and then treated with a 1N aqueous hydrochloric acid solution (10 mL). The layers were shaken and separated. The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford 2-(3,4-bis-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid (1.10 g, 98%) as a white foam which was used without further purification: mp 64-68°C (foam to gel); FAB-HRMS *m/e* calcd for  $C_{16}H_{22}O_6S_2$  ( $M+H$ )<sup>+</sup> 375.0936, found 375.0932.

A solution of triphenylphosphine (154 mg, 0.59 mmol) in methylene chloride (2 mL) was cooled to 0°C and then slowly treated with *N*-bromosuccinimide (105 mg, 0.59 mmol). The reaction mixture was stirred at 0°C for 10 min and then treated with 2-(3,4-bis-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid (200 mg, 0.53 mmol). The resulting reaction mixture was stirred at 0°C for 5 min and then allowed to warm to 25°C where it was stirred for 30 min. The reaction mixture was then treated with 2-aminopyridine (110 mg, 1.18 mmol). The resulting reaction mixture was stirred at 25°C



## Example 82

## 3-Cyclopentyl-2-(4-sulfamoyl-phenyl)-N-thiazol-2-yl-propionamide



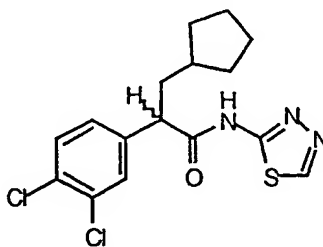
A solution of diisopropylamine (3.3 mL, 23.5 mmol) in dry tetrahydrofuran (50 mL) and  
5 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (10 mL) was cooled to -78°C under  
nitrogen and then treated with a 10M solution of n-butyllithium in hexanes (2.35 mL,  
23.5 mmol). The yellow reaction mixture was stirred at -78°C for 30 min and then  
treated dropwise with a solution of 4-methylsulfonylphenylacetic acid (2.40 g, 11.2  
mmol) in a small amount of dry tetrahydrofuran. After approximately one-half of the 4-  
10 methylsulfonylphenylacetic acid in dry tetrahydrofuran was added, a precipitate formed.  
Upon further addition of the remaining 4-methylsulfonylphenylacetic acid in dry  
tetrahydrofuran, the reaction mixture became thick in nature. After complete addition of  
the 4-methylsulfonylphenylacetic acid in dry tetrahydrofuran, the reaction mixture was  
very thick and became difficult to stir. An additional amount of dry tetrahydrofuran (20  
15 mL) was added to the thick reaction mixture, and the reaction mixture was stirred at -  
78°C for 45 min, at which time, a solution of iodomethylcyclopentane (2.35 g, 11.2  
mmol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction  
mixture was allowed to warm to 25°C where it was stirred for 15 h. The reaction mixture  
was quenched with water (100 mL), and the resulting yellow reaction mixture was  
20 concentrated *in vacuo* to remove tetrahydrofuran. The aqueous residue was acidified to  
pH = 2 using concentrated hydrochloric acid. The aqueous layer was extracted with ethyl  
acetate. The organic phase was dried over magnesium sulfate, filtered, and concentrated  
*in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/3 hexanes/ ethyl  
acetate) afforded 3-cyclopentyl-2-(4-methanesulfonyl-phenyl)propionic acid (1.80 g,

warm to 25°C. The reaction mixture was stirred at 25°C for 30 min then heated under reflux for 20 h. The reaction mixture was cooled to 0°C and then treated with water (3 mL) followed by sodium acetate (702.5 mg, 8.56 mmol) and then finally hydroxylamine-O-sulfonic acid (484.2 mg, 4.28 mmol). The resulting reaction mixture was stirred at 0°C for 30 min then allowed to warm to 25°C where it was stirred for 44 h. The reaction mixture was concentrated *in vacuo* to remove tetrahydrofuran. The resulting aqueous residue was diluted with ethyl acetate (150 mL). The organic layer was washed with a saturated aqueous sodium bicarbonate solution (1 x 100 mL) and a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/2 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-sulfamoyl-phenyl)-N-thiazol-2-yl-propionamide (191.8 mg, 72%) as a white solid: mp 179-181°C; EI-HRMS *m/e* calcd for C<sub>17</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub>S<sub>2</sub> (M<sup>+</sup>) 379.1024, found 379.1029.

15

## Example 85

## 3-Cyclopentyl-2-(3,4-dichlorophenyl)-N-[1,3,4]thiadiazol-2-yl-propionamide



A solution of 3-cyclopentyl-2-(3,4-dichlorophenyl)-propionic acid (prepared from Example 38, 200.0 mg, 0.70 mmol), O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (316.9 mg, 0.84 mmol), N,N-diisopropylethylamine (365 mL, 2.09 mmol), and 2-amino-1,3,4-thiadiazole (140.8 mg, 1.39 mmol) in dry N,N-dimethylformamide (2 mL) was stirred at 25°C under nitrogen for 20 h. The reaction mixture was concentrated *in vacuo* to remove N,N-dimethylformamide. The resulting residue was diluted with ethyl acetate (100 mL). The organic layer was washed with a

ester (1.60 g, 79.3%) as a clear oil: EI-HRMS m/e calcd for  $C_{15}H_{19}O_2Br$  ( $M^+$ ) 310.0568 found 310.0564.

A solution of 2-(4-bromo-phenyl)-3-cyclopentyl-propionic acid methyl ester (500 mg, 1.60 mmol) in *N,N*-dimethylformamide (4.01 mL) was treated with copper(I) cyanide (144 mg, 1.60 mmol). The mixture was heated at 170°C for 1 h. At this time, the reaction was cooled to 25°C and poured into aqueous ammonium hydroxide (5 mL). The solution was diluted with water (25 mL) and extracted with ethyl acetate (3 x 35 mL). The organics were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 90/10 hexanes/ethyl acetate) afforded 2-(4-cyano-phenyl)-3-cyclopentyl-propionic acid methyl ester (65.6 g, 15.8%) as a clear oil: EI-HRMS m/e calcd for  $C_{16}H_{19}NO_2$  ( $M^+$ ) 257.1415 found 257.1406.

A solution of 2-(4-cyano-phenyl)-3-cyclopentyl-propionic acid methyl ester (65.0 mg; 0.25 mmol) in tetrahydrofuran/water/methanol (2.5 mL, 3:1:1) was treated with a 1N aqueous lithium hydroxide solution (0.27 mL, 0.27 mmol). The reaction was stirred at 25°C for 6 h. At this time, the reaction was acidified to pH = 1 with a 1N aqueous hydrochloric acid solution and extracted with chloroform/methanol (9:1, 3 x 25 mL). The organics were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 80/20 hexanes/ethyl acetate) afforded 2-(4-cyano-phenyl)-3-cyclopentyl-propionic acid (36.0 mg, 58.6%) as a white solid: mp 126-128°C; EI-HRMS m/e calcd for  $C_{15}H_{17}NO_2$  ( $M^+$ ) 243.1259 found 243.1268.

A solution of 2-(4-cyano-phenyl)-3-cyclopentyl-propionic acid (33.0 mg, 0.13 mmol) in methylene chloride (1.36 mL) was cooled to 0°C and then treated with a 2.0M solution of oxalyl chloride in methylene chloride (0.07 mL, 0.14 mmol) and a few drops of *N,N*-dimethylformamide. The reaction mixture was stirred at 0°C for 10 min and at 25°C for

3.7 mmol) was then added in hexamethylphosphoramide (1 mL). The reaction mixture was stirred at -78°C for 4 h. The reaction was then warmed to 25°C and was stirred at 25°C for 16 h. The reaction mixture was then quenched by the dropwise addition of saturated aqueous ammonium chloride solution (10 mL). The excess solvent was removed *in vacuo*. The residue was acidified to pH = 1 with a 1N aqueous hydrochloric acid solution. The mixture was poured into water (150 mL) and extracted with ethyl acetate (3 x 100 mL). The organics were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 95/5 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-trifluoromethyl-phenyl)-propionic acid  
10 (634.9 mg, 65%) as a white solid; mp 94-95°C; FAB-HRMS *m/e* calcd for C<sub>15</sub>H<sub>17</sub>F<sub>3</sub>O<sub>2</sub> (M+Na)<sup>+</sup> 309.1079, found 309.1072.

A solution of benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (170 mg, 0.38 mmol), 3-cyclopentyl-2-(4-trifluoromethyl-phenyl)-propionic acid (100 mg, 0.34 mmol), and 2-aminopyridine (36 mg, 0.38 mmol) in *N,N*-dimethylformamide (1.75 mL) was treated with *N,N*-diisopropylethylamine (0.12 mL, 0.73 mmol). The reaction mixture was stirred at 25°C for 18 h. At this time, the reaction was poured into water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with a 1N aqueous hydrochloric acid solution (1 x  
20 50 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 90/10 hexanes/ethyl acetate) afforded 3-cyclopentyl-*N*-pyridin-2-yl-2-(4-trifluoromethyl-phenyl)-propionamide (127 mg, 53.3%) as a white gum; EI-HRMS *m/e* calcd for C<sub>20</sub>H<sub>21</sub>F<sub>3</sub>N<sub>2</sub>O (M<sup>+</sup>) 362.1605, found 362.1592.

25

(B) In an analogous manner, there was obtained:

(a) From 6-amino-nicotinic acid methyl ester and 3-cyclopentyl-2-(4-trifluoromethyl-phenyl)-propionic: 6-[3-Cyclopentyl-2-(4-trifluoromethyl-phenyl)-propionylamino]-

The reaction mixture was stirred under hydrogen gas at 60 psi at 25°C for 18 h. The catalyst was then filtered off through a pad of celite (ethyl acetate). The filtrate was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate) afforded 2-(4-amino-phenyl)-3-cyclopentyl-propionic acid ethyl ester (3.52 mg, 53.3%) as a yellow oil: EI-HRMS *m/e* calcd for  $C_{16}H_{23}NO_2$  ( $M^+$ ) 261.1729 found 261.1727.

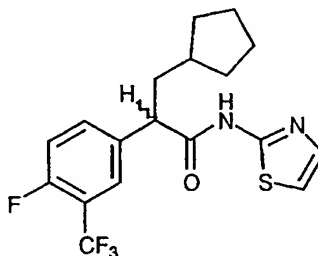
A mixture of concentrated hydrochloric acid (0.38 mL) and ice (380 mg) cooled to 0°C was treated with 2-(4-amino-phenyl)-3-cyclopentyl-propionic acid ethyl ester (497 mg, 1.90 mmol). After 5 min, a solution of sodium nitrite (139 mg, 2.01 mmol) in water (0.31 mL) was added to the reaction mixture. The resulting solution was stirred at 0°C for 5 min. At this time, the solution was added to a solution of *n*-butyl mercaptan (0.23 mL, 2.20 mmol) in water (0.41 mL) warmed to 45°C. The reaction was stirred at 45°C for 3 h. At this time, the reaction was diluted with water (50 mL) and extracted with chloroform (3 x 50 mL). The organics were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude brown oil (588 mg) in methylene chloride (8.8 mL) was cooled to 0°C and treated with 3-chloroperoxybenzoic acid (80-85% grade, 1.5 g, 8.78 mmol). The reaction mixture was stirred at 25°C for 18 h. At this time, the reaction was diluted with water (75 mL) and extracted with chloroform (2 x 30 mL). The organics were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 80/20 hexanes/ethyl acetate) afforded 2-[4-(butane-1-sulfonyl)-phenyl]-3-cyclopentyl-propionic acid ethyl ester (144.3 mg, 20.7%) as a yellow oil: EI-HRMS *m/e* calcd for  $C_{20}H_{30}O_4S$  ( $M^+$ ) 366.1865 found 366.1858.

25

A solution of 2-[4-(butane-1-sulfonyl)-phenyl]-3-cyclopentyl-propionic acid ethyl ester (140 mg, 0.38 mmol in tetrahydrofuran/water/methanol (0.95 mL, 3:1:1) was treated with a 1N aqueous lithium hydroxide solution (0.76 mL, 0.76 mmol). The reaction was stirred at 25°C for 8 h. At this time, the reaction was acidified to pH = 1 with a 1N aqueous

## Example 89

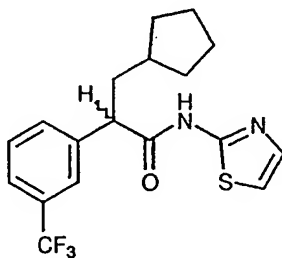
## (A) 3-Cyclopentyl-2-(4-fluoro-3-trifluoromethyl-phenyl)-N-thiazol-2-yl-propionamide



- 5 A solution of freshly prepared lithium diisopropylamide (35.32 mL of a 0.31M stock solution, 10.95 mmol) cooled to  $-78^{\circ}\text{C}$  was treated with (4-fluoro-3-trifluoromethyl-phenyl)-acetic acid (1.11 g, 5.0 mmol) in tetrahydrofuran/1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (12.42 mL, 3:1). The resulting solution was stirred at  $-78^{\circ}\text{C}$  for 1 h. Iodomethylcyclopentane (1.16 g, 5.52 mmol) was then added in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (1.2 mL). The reaction mixture was stirred at  $-78^{\circ}\text{C}$  for 4
- 10 h. The reaction was then warmed to  $25^{\circ}\text{C}$  and was stirred at  $25^{\circ}\text{C}$  for 24 h. This solution was then quenched by the slow addition of the reaction mixture to a 2N aqueous hydrochloric acid solution (50 mL). The product was extracted into ethyl acetate (1 x 300 mL) and diethyl ether (1 x 50 mL). The organics were dried over sodium sulfate, filtered,
- 15 and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-fluoro-3-trifluoromethyl-phenyl)-propionic acid (1.28 g, 84.3%) as a white solid: mp  $65-68^{\circ}\text{C}$ ; EI-HRMS  $m/e$  calcd for  $\text{C}_{15}\text{H}_{16}\text{F}_4\text{O}_2$  ( $\text{M}^+$ ) 305.1165, found 305.1174.
- 20 A solution of 3-cyclopentyl-2-(4-fluoro-3-trifluoromethyl-phenyl)-propionic acid (304 mg, 1.0 mmol) in methylene chloride (10 mL) was cooled to  $0^{\circ}\text{C}$  and then treated with a 2.0M solution of oxalyl chloride in methylene chloride (0.6 mL, 1.2 mmol) and a few drops of *N,N*-dimethylformamide. The reaction mixture was stirred at  $0^{\circ}\text{C}$  for 15 min and at  $25^{\circ}\text{C}$  for 24 h. The reaction mixture was then treated with 2-amino-thiazole (175

## Example 90

## 3-Cyclopentyl-N-thiazol-2-yl-2-(3-trifluoromethyl-phenyl)-propionamide



A solution of freshly prepared lithium diisopropylamide (35.32 mL of a 0.31M stock  
5 solution, 10.9 mmol) cooled to  $-78^{\circ}\text{C}$  was treated with (3-trifluoromethyl-phenyl)-acetic  
acid (1.02 g, 5.0 mmol) in tetrahydrofuran/1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-  
pyrimidinone (12.4 mL, 3:1). The resulting solution was stirred at  $-78^{\circ}\text{C}$  for 3 h.  
Iodomethylcyclopentane (1.16 g, 5.52 mmol) was then added in 1,3-dimethyl-3,4,5,6-  
tetrahydro-2(1H)-pyrimidinone (1.16 mL). The reaction mixture was stirred at  $-78^{\circ}\text{C}$  for  
10 4 h. The reaction was then warmed to  $25^{\circ}\text{C}$  and was stirred at  $25^{\circ}\text{C}$  for 48 h. This  
solution was then quenched by the slow addition of the reaction mixture to a 2N aqueous  
hydrochloric acid solution (50 mL). The product was extracted into ethyl acetate (3 x 100  
mL) and diethyl ether (1 x 50 mL). The organics were washed with a saturated aqueous  
lithium chloride solution (2 x 100 mL) and a saturated aqueous sodium chloride solution  
15 (1 x 150 mL), dried over magnesium sulfate and sodium sulfate, filtered, and  
concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50  
hexanes/ethyl acetate with acetic acid) afforded 3-cyclopentyl-2-(3-trifluoromethyl-  
phenyl)-propionic acid (1.16 g, 80.5%) as an off-white solid: mp  $64-65^{\circ}\text{C}$ ; EI-HRMS *m/e*  
calcd for  $\text{C}_{15}\text{H}_{17}\text{F}_3\text{O}_2$  ( $\text{M} + \text{Na}^+$ ) 309.1079, found 309.1084.

20

A solution of 3-cyclopentyl-2-(3-trifluoromethyl-phenyl)-propionic acid (286 mg, 1.0  
mmol) in methylene chloride (10 mL) was cooled to  $0^{\circ}\text{C}$  and then treated with a 2.0M  
solution of oxalyl chloride in methylene chloride (0.6 mL, 1.2 mmol) and a few drops of  
*N,N*-dimethylformamide. The reaction mixture was stirred at  $0^{\circ}\text{C}$  for 15 min and at  $25^{\circ}\text{C}$

*vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate with acetic acid) afforded 3-cyclopentyl-2-(4-fluoro-3-trifluoromethyl-phenyl)-propionic acid (1.28 g, 84.3%) as a white solid: mp 66-68°C; EI-HRMS *m/e* calcd for  $C_{15}H_{16}F_4O_2$  ( $M^+$ ) 305.1165, found 305.1174.

5

A solution of 3-cyclopentyl-2-(4-fluoro-3-trifluoromethyl-phenyl)-propionic acid (7.77 g, 25.3 mmol) in methanol (50 mL) was treated slowly with concentrated sulfuric acid (0.01 mL). The resulting reaction mixture was heated under reflux for 24 h. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo*. The residue was dissolved in ethyl acetate (75 mL) and washed with a saturated aqueous sodium bicarbonate solution (1 x 50 mL), water (1 x 50 mL), and a saturated aqueous sodium chloride solution (4 x 50 mL). The organics were dried over magnesium sulfate and sodium sulfate, filtered, and concentrated *in vacuo* to afford 3-cyclopentyl-2-(4-fluoro-3-trifluoromethyl-phenyl)-propionic acid methyl ester (8.48 g, 87.5%) as yellow oil: EI-HRMS *m/e* calcd for  $C_{16}H_{18}F_4O_2$  ( $M^+$ ) 318.1243, found 318.1240.

10  
15

A solution of 3-cyclopentyl-2-(4-fluoro-3-trifluoromethyl-phenyl)-propionic acid methyl ester (7.0 g, 21.9 mmol) in *N,N*-dimethylformamide (50 mL) was treated with sodium methanethiolate (2.61 g, 33.0 mmol). The reaction mixture was then heated at 100-110°C for 24 h. At this time, the reaction was poured onto a mixture of ice and a 2N aqueous hydrochloric acid solution (100 mL). This mixture was extracted into ethyl acetate (3 x 75 mL) and diethyl ether (1 x 50 mL). The organics were then washed with water (1 x 75 mL) and a saturated aqueous sodium chloride solution (3 x 100 mL). The organics were dried over magnesium sulfate and sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 85/15 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-methylsulfanyl-3-trifluoromethyl-phenyl)-propionic acid methyl ester (2.48g, 35.5%) as a pale yellow oil: EI-HRMS *m/e* calcd for  $C_{17}H_{21}F_3O_2S$  ( $M^+$ ) 346.1214, found 346.1212.

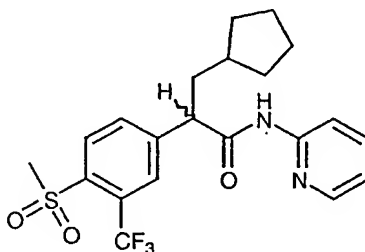
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- (b) From 2-amino-thiazole-4-carboxylic acid methyl ester and 3-cyclopentyl-2-(4-methanesulfonyl-3-trifluoromethyl-phenyl)-propionic acid: 2-[3-Cyclopentyl-2-(4-methanesulfonyl-3-trifluoromethyl-phenyl)-propionylamino]-thiazole-4-carboxylic acid methyl ester as a white solid: mp 117-121°C; FAB-HRMS m/e calcd for  $C_{21}H_{23}F_3N_2O_5S_2$  (M+H)<sup>+</sup> 504.1000, found 504.1000.

### Example 92

#### 3-Cyclopentyl-2-(4-methanesulfonyl-3-trifluoromethyl-phenyl)-N-pyridin-2-yl-propionamide



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- A solution of freshly prepared lithium diisopropylamide (141.28 mL of a 0.31M stock solution, 43.8 mmol) cooled to -78°C was treated with (4-fluoro-3-trifluoromethyl-phenyl)-acetic acid (4.44 g, 20.0 mmol) in tetrahydrofuran/1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (49.68 mL, 3:1). The resulting solution was stirred at -78°C for 1 h. At this time, the reaction was treated with a solution of iodomethylcyclopentane (4.64 g, 22.09 mmol) in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (4.6 mL). The reaction mixture was stirred at -78°C for 4 h. The reaction was then warmed to 25°C and was stirred at 25°C for 48 h. This solution was then quenched by the slow addition of the reaction mixture to a 2N aqueous hydrochloric acid solution. The product was extracted into ethyl acetate (3 x 400 mL) and diethyl ether (1 x 200 mL). The organics were dried over magnesium sulfate and sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate with acetic acid) afforded 3-cyclopentyl-2-(4-fluoro-3-

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chloroperoxybenzoic acid (80-85% grade, 4.8 g, 19.8 mmol). The reaction mixture was stirred at 25°C for 4 d. At this time, the reaction was diluted with methylene chloride (25 mL). This solution was washed with a saturated aqueous sodium bisulfite solution (1 x 50 mL), water (1 x 50 mL), a saturated aqueous sodium bicarbonate solution (1 x 50 mL),  
5 water (1 x 50 mL), and a saturated aqueous sodium chloride solution (3 x 50 mL). The organics were dried over magnesium sulfate and sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 70/30 hexanes/ethyl acetate with acetic acid) afforded 3-cyclopentyl-2-(4-methanesulfonyl-3-trifluoromethyl-phenyl)-propionic acid ethyl ester (1.28 g, 89.0%) as a clear oil: EI-  
10 HRMS *m/e* calcd for  $C_{18}H_{23}F_3O_4S$  ( $M^+$ ) 392.1269 found 392.1268.

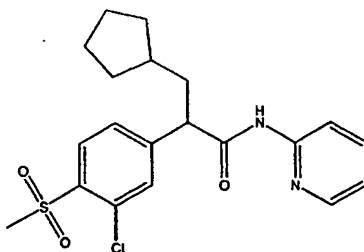
A solution of 3-cyclopentyl-2-(4-methanesulfonyl-3-trifluoromethyl-phenyl)-propionic acid ethyl ester (707mg, 1.80 mmol in tetrahydrofuran/water (24 mL, 3:1) was treated with lithium hydroxide (166 mg, 3.97 mmol). The reaction was stirred at 25°C for 24 h.  
15 At this time, the reaction concentrated *in vacuo*. The residue was diluted with water (25 mL) and extracted with diethyl ether (1 x 15 mL). The aqueous layer was acidified to pH = 1 with a 2N aqueous hydrochloric acid solution, and extracted with chloroform (3 x 25 mL). The organics were washed with water (1 x 25 mL), a saturated aqueous sodium chloride solution (3 x 25 mL), dried over magnesium sulfate, filtered, and concentrated *in*  
20 *vacuo* to afford 3-cyclopentyl-2-(4-methanesulfonyl-3-trifluoromethyl-phenyl)-propionic acid (426.7 mg, 65%) as a white solid: mp 122-123°C; EI-HRMS *m/e* calcd for  $C_{16}H_{19}F_3O_4S$  ( $M^+$ ) 364.0956 found 364.0956.

A solution of and 3-cyclopentyl-2-(4-methanesulfonyl-3-trifluoromethyl-phenyl)-  
25 propionic acid (73 mg, 0.2 mmol) and triphenylphosphine (79 mg, 0.3 mmol) in methylene chloride (5.0 mL) was cooled to 0°C and then treated with *N*-bromosuccinimide (60.5 mg, 0.34 mmol). After the complete addition of *N*-bromosuccinimide, the reaction mixture was allowed to warm to 25°C over 30 min. The reaction mixture was then treated with 2-aminopyridine (28.2 mg, 0.3mmol) and pyridine

A solution of benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (188 mg, 0.42 mmol) and 3-cyclopentyl-2-(4-methylsulfanyl-3-trifluoromethyl-phenyl)-propionic acid (94 mg, 0.28 mmol) in *N,N*-dimethylformamide (5 mL) was treated with *N,N*-diisopropylethylamine (150  $\mu$ L, 0.85 mmol) and 2-aminothiazole (42.5 mg, 0.42 mmol). The mixture was stirred at 25°C for 48 h. At this time, the reaction mixture was poured into cold water (25 mL) containing a 1N aqueous hydrochloric acid solution (50 mL) and extracted into ethyl acetate (2 x 75 mL) and diethyl ether (1 x 25 mL). The organics were then washed with water (2 x 75 mL) and a saturated aqueous sodium chloride solution (3 x 75 mL), dried over magnesium sulfate and sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-methylsulfanyl-3-trifluoromethyl-phenyl)-N-thiazol-2-yl-propionamide (50.5 mg, 43.1%) as a clear oil: FAB-HRMS *m/e* calcd for  $C_{19}H_{21}F_3N_2OS_2$  (M+H)<sup>+</sup> 415.1125, found 415.1123.

#### Example 94

##### 2-(3-Chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide



A solution of aluminum trichloride (34.8 g, 261.4 mmol) in chloroform (120 mL) under argon and cooled to 0°C and was then treated dropwise with a solution of ethyl chlorooxoacetate (18.7 mL, 167.5 mmol) in chloroform (120 mL). The mixture was then stirred at 0°C for 30 min. After this time a solution of 2-chlorothioanisole (25.0 g, 156.5 mmol) in chloroform (120 mL) was added dropwise to the above mixture at 0°C and it

acrylic acid ethyl ester (95 mg, 86%, mixture of E and Z isomers (2:1)) as a colorless oil and taken on without characterization.

The mixture of E and Z isomers of 2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-  
5 acrylic acid ethyl ester (1.04 g, 2.91 mmol), nickel chloride hexahydrate (69 mg, 0.29 mmol) and methanol (25 mL) were placed in a flask under argon. To this green solution was then added sodium borohydride (221 mg, 5.83 mmol) slowly in small portions using an ice bath if necessary to keep the temperature at 20°C. The solution turned black and a fine precipitate formed after addition of the sodium borohydride. This was then stirred at  
10 25°C for 1.5 h. After such time the reaction was filtered through celite and washed with methanol. The filtrate and washings were combined and concentrated *in vacuo* to reduce the volume. The residual solution was then diluted with water (15 mL) and extracted with ethyl acetate (3 x 15 mL) dried over sodium sulfate, filtered and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 75/25 hexanes/ethyl  
15 acetate) afforded a mixture of 2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid methyl ester and 2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid ethyl ester (transesterification occurred under the reaction conditions) (937 mg) as a clear colorless oil. (It was carried on without characterization because it was a mixture of esters)

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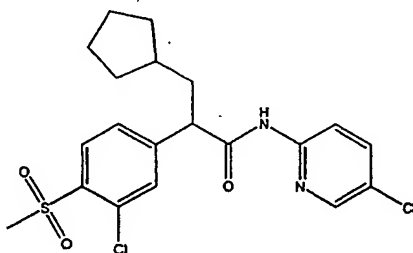
The mixture of 2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid methyl ester and 2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid ethyl ester, from above, (937 mg) was dissolved in ethanol (30 mL) and allowed to dissolve. To this solution was then added a solution of potassium hydroxide (733 mg,  
25 13.1 mmol) in water (7 mL). The yellow solution was then stirred for 3 h at 25°C. It was concentrated *in vacuo* to remove the ethanol and then 1N hydrochloric acid was added until the pH = 2. This was then extracted with methylene chloride (3 X 15 mL). The organic layers were then dried over sodium sulfate, filtered and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 75/25 hexanes/ethyl acetate

reaction mixture was stirred at 0°C until it was completely dissolved and became light purple in color. The reaction mixture was then treated with 2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid (prepared in Example 94; 200 mg, 0.61 mmol) and stirred at 0°C for 20 min and then warmed to 25°C where it was stirred  
5 for 30 min. After such time, the reaction mixture was treated with 2-amino-5-bromopyridine (157 mg, 0.91 mmol) and pyridine (0.088 mL, 1.09 mmol), and reaction mixture was stirred at 25°C for 16 h. The reaction was then diluted with water (10 mL) and then extracted with methylene chloride (3 x 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash  
10 chromatography (Merck Silica gel 60, 230-400 mesh, 70/30 hexanes/ethyl acetate) afforded 2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-N-(5-bromo-pyridin-2-yl)-propionamide (245 mg, 83%) as a white foam: EI-HRMS *m/e* calcd for C<sub>20</sub>H<sub>22</sub>BrClN<sub>2</sub>O<sub>3</sub>S (M<sup>+</sup>) 484.0223, found 484.0222.

15

**Example 96**

**N-(5-Chloro-pyridin-2-yl)-2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionamide**

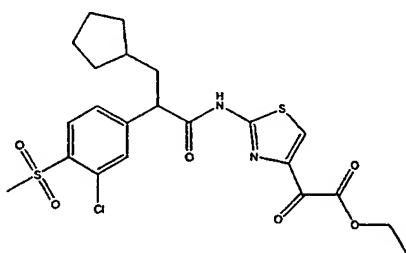


A solution of triphenylphosphine (238 mg, 0.91 mmol) in methylene chloride (10 mL)  
20 was cooled to 0°C and then treated with *N*-bromosuccinimide (183 mg, 1.03 mmol). The reaction mixture was stirred at 0°C until it was completely dissolved and became light purple in color. The reaction mixture was then treated with 2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid (prepared in Example 94, 200 mg, 0.61 mmol) and stirred at 0°C for 20 min and then warmed to 25°C where it was stirred

organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 60/40 hexanes/ethyl acetate) afforded 2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide (122 mg, 43%) as a white foam: EI-HRMS *m/e* calcd for  $C_{20}H_{22}ClF_3N_2O_3S$  ( $M^+$ ) 474.0992, found 474.0990.

### Example 98

{2-[2-(3-Chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionylamino]-thiazol-4-yl}-oxo-acetic acid ethyl ester



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A solution of triphenylphosphine (238 mg, 0.91 mmol) in methylene chloride (10 mL) was cooled to 0°C and then treated with *N*-bromosuccinimide (183 mg, 1.03 mmol). The reaction mixture was stirred at 0°C until it was completely dissolved and became light purple in color. The reaction mixture was then treated with 2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid (prepared in Example 94, 200 mg, 0.61 mmol) and stirred at 0°C for 20 min and then warmed to 25°C where it was stirred for 30 min. After such time, the reaction mixture was treated with 2-(amino-thiazol-4-yl)-oxo-acetic acid ethyl ester (182 mg, 0.91 mmol) and pyridine (0.088 mL, 1.09 mmol), and the reaction mixture was stirred at 25°C for 16 h. The reaction was then diluted with water (10 mL) and then extracted with methylene chloride (3 x 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 75/25 hexanes/ethyl acetate) afforded {2-[2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionylamino]-

20

25%) as a white foam:  $[\alpha]^{23}_{589} = -93.9^\circ$  ( $c=0.165$ , chloroform); FAB-HRMS  $m/e$  calcd for  $C_{25}H_{28}ClNO_5S$  ( $M+H$ )<sup>+</sup> 490.1455, found 490.1443.

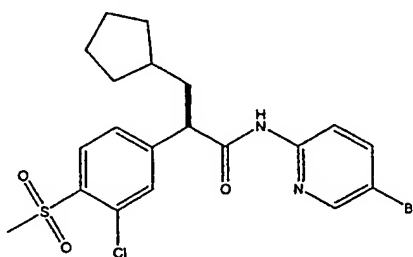
A solution of lithium hydroxide (215 mg, 9.0 mmol) in water (2.8 mL) was treated with a  
5 30% aqueous hydrogen peroxide solution (2.0 mL, 18 mmol). This freshly prepared lithium hydroperoxide solution was then cooled to 0°C and then slowly added to a cooled (0°C) solution of 4(R)-benzyl-3-[2(R)-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionyl]-oxazolidin-2-one (2.20 g, 4.5 mmol) in tetrahydrofuran (18 mL) and water (5.8 mL). After 1.5 h at 0°C, the reaction was quenched with a 1.5N aqueous  
10 sodium sulfite solution (25 mL) and was diluted with water (150 mL). The aqueous layer was extracted with diethyl ether (3 x 50 mL). The aqueous layer was then acidified with a 1N aqueous hydrochloric acid solution to pH = 2 and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 75/25  
15 hexanes/ethyl acetate with 1% acetic acid) afforded 2(R)-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid (1.26 g, 85%) as a white solid: mp 106.1-108.8°C;  $[\alpha]^{23}_{589} = -43.0^\circ$  ( $c=0.172$ , chloroform); EI-HRMS  $m/e$  calcd for  $C_{15}H_{19}ClO_4S$  ( $M^+$ ) 330.0692, found 330.0690.

20 A solution of triphenylphosphine (248 mg, 0.94 mmol) in methylene chloride (9 mL) was cooled to 0°C and then treated with *N*-bromosuccinimide (190 mg, 1.07 mmol). The reaction mixture was stirred at 0°C until it was completely dissolved and became light purple in color. The reaction mixture was then treated with 2(R)-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid (208 mg, 0.63 mmol). The  
25 reaction mixture was stirred at 0°C for 20 min and then warmed to 25°C where it was stirred for 30 min. After such time, the reaction mixture was treated with 2-aminothiazole (95 mg, 0.94 mmol) and pyridine (0.092 mL, 1.13 mmol), and the reaction mixture was stirred at 25°C for 16 h. The reaction was then diluted with water (10 mL) and then extracted with methylene chloride (3 x 15 mL). The combined organic layers

81.5%) as a white foam:  $[\alpha]_{589}^{23} = -41.8^\circ$  ( $c=0.098$ , chloroform); EI-HRMS  $m/e$  calcd for  $C_{20}H_{23}ClN_2O_3S$  ( $M^+$ ) 406.1118, found 406.1119.

### Example 101

5    **N-(5-Bromo-pyridin-2-yl)-2(R)-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionamide**



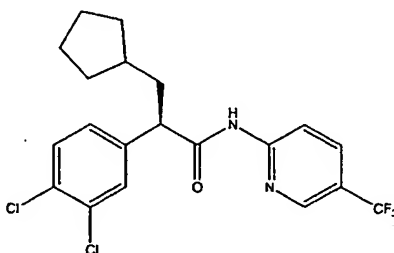
A solution of triphenylphosphine (238 mg, 0.91 mmol) in methylene chloride (10 mL) was cooled to  $0^\circ\text{C}$  and then treated with *N*-bromosuccinimide (183 mg, 1.03 mmol). The reaction mixture was stirred at  $0^\circ\text{C}$  until it was completely dissolved and became light purple in color. The reaction mixture was then treated with 2(R)-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid (prepared in Example 99, 200 mg, 0.61 mmol). The reaction mixture was stirred at  $0^\circ\text{C}$  for 20 min and then warmed to  $25^\circ\text{C}$  where it was stirred for 30 min. After such time, the reaction mixture was treated with 2-aminopyridine (85 mg, 0.91 mmol) and pyridine (0.088 mL, 1.09 mmol), and the reaction mixture was stirred at  $25^\circ\text{C}$  for 16 h. The reaction was then diluted with water (10 mL) and then extracted with methylene chloride (3 x 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Biotage chromatography (FLASH 40S, Silica, 60/40 hexanes/ethyl acetate) afforded N-(5-bromo-pyridin-2-yl)-2(R)-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionamide (222 mg, 76%) as an off-white foam:  $[\alpha]_{589}^{23} = -48.6^\circ$  ( $c=0.105$ , chloroform); EI-HRMS  $m/e$  calcd for  $C_{20}H_{22}BrClN_2O_3S$  ( $M^+$ ) 484.0223, found 484.0223.



were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 85/15 hexanes/ethyl acetate) afforded N-(5-cyano-pyridin-2-yl)-3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionamide (882 mg, 73%) as a pink foam: EI-HRMS *m/e* calcd for C<sub>20</sub>H<sub>19</sub>Cl<sub>2</sub>N<sub>3</sub>O (M<sup>+</sup>) 387.0905, found 387.0905.

### Example 103

#### 3-Cyclopentyl-2(R)-(3,4-dichloro-phenyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide



10

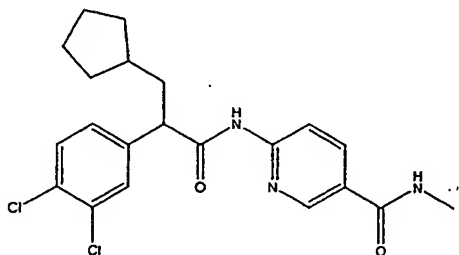
A solution of 3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionic acid (prepared in Example 54, 200 mg, 0.69 mmol) in methylene chloride (10 mL) and one drop of *N,N*-dimethylformamide was cooled to 0°C and then treated with a 2.0M solution of oxalyl chloride in methylene chloride (0.42 mL, 0.84 mmol). Gas evolution began immediately.

15 The reaction mixture was allowed to warm slowly to 25°C where it was stirred for 30 min. After this time, the reaction mixture was treated with a solution of *N,N*-diisopropylethylamine (0.24 mL, 1.39 mmol) and 5-trifluoromethyl-2-aminopyridine (150 mg, 0.905 mmol) in tetrahydrofuran (4 mL) in one portion. The resulting reaction mixture was stirred for 16 h at 25°C. After such time, the reaction was diluted with water

20 (15 mL) and was extracted with methylene chloride (3 x 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 90/10 hexanes/ethyl acetate) afforded the 3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-N-(5-trifluoromethyl-pyridin-2-yl)-

## Example 105

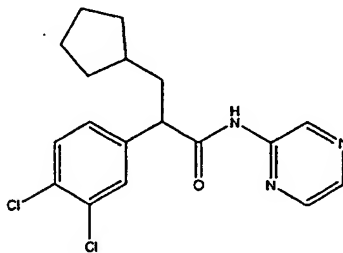
## 6-[3-Cyclopentyl-2-(3,4-dichloro-phenyl)-propionylamino]-N-methyl-nicotinamide



A solution of 6-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionylamino]-nicotinic acid  
5 (prepared in Example 46, 125 mg, 0.31 mmol), *N,N*-diisopropylethylamine (0.10 mL,  
0.61 mmol), and benzotriazol-1-yloxy-tris(dimethylamino)phosphonium  
hexafluorophosphate (142 mg, 0.32 mmol) in *N,N*-dimethylformamide (15 mL) at 25°C  
was treated dropwise with a 2.0M solution of methylamine in tetrahydrofuran (0.16 mL,  
0.32 mmol). The resulting reaction mixture was stirred at 25°C for 16 h. The reaction  
10 mixture was then diluted with water (10 mL) and extracted with ethyl acetate (3 x 10  
mL). The combined organic layers were dried over sodium sulfate, filtered, and  
concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50  
hexanes/ethyl acetate) afforded 6-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-  
propionylamino]-N-methyl-nicotinamide (83 mg, 64%) as white solid: mp 229.1-  
15 231.7°C; FAB-HRMS *m/e* calcd for  $C_{21}H_{23}Cl_2N_3O_2$  ( $M+H$ )<sup>+</sup> 420.1245, found 420.1247.

## Example 106

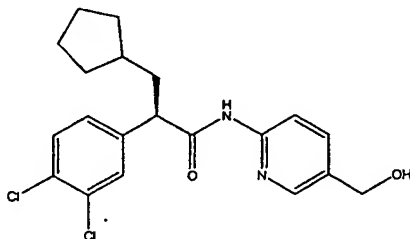
## 3-Cyclopentyl-2-(3,4-dichloro-phenyl)-N-pyrazin-2-yl-propionamide



stirred for 30 min. After such time, the reaction mixture was treated with 2-amino-5-bromopyridine (271 mg, 1.57 mmol) and pyridine (0.15 mL, 1.88 mmol). The resulting reaction mixture was stirred at 25°C for 16 h. The reaction was then diluted with water (10 mL) and extracted with methylene chloride (3 x 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 90/10 hexanes/ethyl acetate) afforded N-(5-bromo-pyridin-2-yl)-3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionamide (448 mg, 97%) as a white solid: mp 107.3-109.9°C;  $[\alpha]_{589}^{23} = -66.7^\circ$  (c=0.084, chloroform); EI-HRMS m/e calcd for C<sub>19</sub>H<sub>19</sub>BrCl<sub>2</sub>N<sub>2</sub>O (M<sup>+</sup>) 440.0058, found 440.0056.

### Example 108

#### 3-Cyclopentyl-2(R)-(3,4-dichloro-phenyl)-N-(5-hydroxymethyl-pyridin-2-yl)propionamide



15

A solution of 6-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionylamino]-nicotinic acid methyl ester (prepared in Example 45, 398 mg, 0.95 mmol) in diethyl ether (30 mL) was cooled to 0°C and then treated with lithium aluminum hydride (54 mg, 1.4 mmol) in one portion. There was immediate gas evolution. The reaction mixture was allowed to slowly warm to 25°C and was stirred at 25°C 16 h. After such time, the reaction mixture was diluted with water (10 mL) and then extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 90/10 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(3,4-dichloro-phenyl)-N-(5-hydroxymethyl-pyridin-2-

20

the iodine solution, the cooling bath was removed, and the reaction mixture was allowed to warm to 25°C where it was stirred for 2 h. The reaction mixture was then poured into a solution consisting of a saturated aqueous ammonium chloride solution (400 mL) and ammonium hydroxide (100 mL), and the organic compound was extracted into ethyl acetate (3 x 200 mL). The combined organic extracts were successively washed with a saturated aqueous sodium thiosulfate solution (1 x 400 mL) and a saturated aqueous sodium chloride solution (1 x 400 mL). The organic layer was then dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 20/1 to 10/1 hexanes/diethyl ether) afforded (E)-3-cycloheptyl-2-iodo-acrylic acid methyl ester (17.86 g, 64%) as a colorless oil: EI-HRMS m/e calcd for C<sub>11</sub>H<sub>17</sub>IO<sub>2</sub> (M<sup>+</sup>) 308.0273, found 308.0273.

A mixture of zinc dust (2.6 g, 40 mmol, Aldrich, -325 mesh) and dry tetrahydrofuran (3 mL) under argon was treated with 1,2-dibromoethane (0.38 g, 2 mmol). The zinc suspension was then heated with a heat gun to ebullition, allowed to cool, and heated again. This process was repeated three times to make sure the zinc dust was activated. The activated zinc dust suspension was then treated with trimethylsilyl chloride (220 mg, 2 mmol), and the suspension was stirred for 15 min at 25°C. The reaction mixture was then treated dropwise with a solution of (E)-3-cycloheptyl-2-iodo-acrylic acid methyl ester (6.16 g, 20 mmol) in dry tetrahydrofuran (5 mL) over 10 min. The reaction mixture was then stirred at 40-45°C for 1 h and then stirred overnight at 25°C. The reaction mixture was then diluted with dry tetrahydrofuran (10 mL), and the stirring was stopped to allow the excess zinc dust to settle down (~2 h). In a separate reaction flask, bis(dibenzylideneacetone)palladium(0) (270 mg, 0.5 mmol) and triphenylphosphine (520 mg, 2 mmol) in dry tetrahydrofuran (25 mL) was stirred at 25°C under argon for 10 min and then treated with 4-bromophenyl methyl sulfone (4.23 g, 18 mmol) and the freshly prepared zinc compound in tetrahydrofuran. The resulting brick red solution was heated at 50°C for 24 h. The reaction mixture was cooled to 25°C and then poured into a saturated aqueous ammonium chloride solution (150 mL), and the organic compound was extracted into ethyl acetate (3 x 150 mL). The combined organic extracts were washed

chloride solution (1 x 50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to afford 3-cycloheptyl-2-(4-methanesulfonyl-phenyl)-propionic acid (78 mg, 86%) as a white solid: EI-HRMS *m/e* calcd for  $C_{17}H_{24}O_4S$  ( $M+H$ )<sup>+</sup> 325.1474, found 325.1478.

5

A solution of triphenylphosphine (116 mg, 0.44 mmol) in methylene chloride (2 mL) was cooled to 0°C and then treated with *N*-bromosuccinimide (78 mg, 0.44 mmol). The reaction mixture was stirred at 0°C for 30 min and then treated with a solution of 3-cycloheptyl-2-(4-methanesulfonyl-phenyl)-propionic acid (72 mg, 0.22 mmol) in  
10 methylene chloride (2 mL). The clear solution was stirred for 10 min at 0°C and then allowed to warm to 25°C where it was stirred for 1.5 h. The reaction mixture was then treated with 2-aminothiazole (66 mg, 0.66 mmol), and the resulting suspension was stirred for 20 h at 25°C. The reaction mixture was then concentrated *in vacuo* to remove methylene chloride, and the residue was diluted with ethyl acetate (30 mL) and a 1N  
15 aqueous hydrochloric acid solution (30 mL). The two layers were separated, and the aqueous layer was extracted with ethyl acetate (1 x 10 mL). The combined organic extracts were successively washed with a saturated aqueous sodium bicarbonate solution (1 x 20 mL) and a saturated aqueous sodium chloride solution (1 x 30 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Biotage  
20 chromatography (FLASH 40S, Silica, 4/1 to 1/1 hexanes/ethyl acetate) afforded 3-cycloheptyl-2-(4-methanesulfonyl-phenyl)-*N*-thiazol-2-yl-propionamide (68 mg, 76%) as an amorphous solid: EI-HRMS *m/e* calcd for  $C_{20}H_{26}N_2O_3S_2$  ( $M^+$ ) 406.1426, found 406.1424.

poured into a solution consisting of a saturated aqueous ammonium chloride solution (400 mL) and ammonium hydroxide (100 mL), and the organic compound was extracted into ethyl acetate (3 x 250 mL). The combined organic extracts were successively washed with a saturated aqueous sodium thiosulfate solution (1 x 500 mL) and a saturated aqueous sodium chloride solution (1 x 500 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 9/1 hexanes/diethyl ether) afforded (E)-3-cyclohexyl-2-iodo-acrylic acid methyl ester (26.3 g, 99%) as a light pink oil: EI-HRMS *m/e* calcd for C<sub>10</sub>H<sub>15</sub>IO<sub>2</sub> (M<sup>+</sup>) 294.0117, found 294.0114.

10

A mixture of zinc dust (2.6 g, 40 mmol, Aldrich, -325 mesh) and dry tetrahydrofuran (3 mL) under argon was treated with 1,2-dibromoethane (0.37 g, 2 mmol). The zinc suspension was then heated with a heat gun to ebullition, allowed to cool, and heated again. This process was repeated three times to make sure the zinc dust was activated. The activated zinc dust suspension was then treated with trimethylsilyl chloride (217 mg, 2 mmol), and the suspension was stirred for 15 min at 25°C. The reaction mixture was then treated dropwise with a solution of (E)-3-cyclohexyl-2-iodo-acrylic acid methyl ester (5.88 g, 20 mmol) in dry tetrahydrofuran (5 mL) over 5 min. During the addition, the temperature rose to 50°C. The reaction mixture was then stirred at 40-45°C for 1 h and then stirred overnight at 25°C. The reaction mixture was then diluted with dry tetrahydrofuran (10 mL), and the stirring was stopped to allow the excess zinc dust to settle down (~2 h). In a separate reaction flask, bis(dibenzylideneacetone)palladium(0) (270 mg, 0.5 mmol) and triphenylphosphine (520 mg, 2 mmol) in dry tetrahydrofuran (25 mL) was stirred at 25°C under argon for 10 min and then treated with 4-bromophenyl methyl sulfone (4.23 g, 18 mmol) and the freshly prepared zinc compound in tetrahydrofuran. The resulting brick red solution was heated at 50°C for 24 h, at which time, thin layer chromatography analysis of the reaction mixture indicated the absence of starting material. The reaction mixture was cooled to 25°C and then poured into a saturated aqueous ammonium chloride solution (150 mL), and the organic compound was extracted into ethyl acetate (3 x 100 mL). The combined organic extracts were washed

30

mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to afford 3-cyclohexyl-2-(4-methanesulfonyl-phenyl)-propionic acid (570 mg, 60%) as a white solid: mp 139-143°C; EI-HRMS *m/e* calcd for  $C_{16}H_{22}O_4S$  ( $M^+$ ) 310.1239, found 310.1241.

5

A solution of triphenylphosphine (416 mg, 1.58 mmol) in methylene chloride (8 mL) was cooled to 0°C and then treated with *N*-bromosuccinimide (281 mg, 1.58 mmol). The reaction mixture was stirred at 0°C for 30 min and then treated with a solution of 3-cyclohexyl-2-(4-methanesulfonyl-phenyl)-propionic acid (290 mg, 0.93 mmol) in  
10 methylene chloride (5 mL). The clear solution was stirred for 15 min at 0°C and then allowed to warm to 25°C where it was stirred for 1.5 h. The reaction mixture was then treated with 2-aminothiazole (233 mg, 2.32 mmol), and the resulting suspension was stirred for 20 h at 25°C. The reaction mixture was concentrated *in vacuo* to remove methylene chloride, and the residue was diluted with ethyl acetate (50 mL) and a 1N  
15 aqueous hydrochloric acid solution (50 mL). The two layers were separated, and the aqueous layer was extracted with ethyl acetate (1 x 30 mL). The combined organic extracts were successively washed with a saturated aqueous sodium bicarbonate solution (1 x 50 mL) and a saturated aqueous sodium chloride solution (1 x 50 mL), dried over anhydrous magnesium sulfate, filtered, and, concentrated *in vacuo*. Biotage  
20 chromatography (FLASH 40S, Silica, 4/1 to 1/1 hexanes/ethyl acetate) afforded 3-cyclohexyl-2-(4-methanesulfonyl-phenyl)-*N*-thiazol-2-yl-propionamide (337 mg, 92%) as an amorphous solid: EI-HRMS *m/e* calcd for  $C_{19}H_{24}N_2O_3S_2$  ( $M^+$ ) 392.1228, found 392.1230.

chromatography (Merck Silica gel 60, 230-400 mesh 80/20 hexanes/ ethyl acetate) afforded 3-cyclopentyl-2-(3-nitro-phenyl)-propionic acid methyl ester (1.63 g, 46.8%) as pale yellow oil: EI-HRMS m/e calcd for  $C_{15}H_{19}NO_4$  ( $M^+$ ) 277.1314, found 277.1317.

- 5 A solution of 3-cyclopentyl-2-(3-nitro-phenyl)-propionic acid methyl ester (0.55 g, 2.0 mmol) in tetrahydrofuran/water (12 mL, 3:1) was treated with lithium hydroxide (185 mg, 4.40 mmol). The reaction was stirred at 25°C for 48 h. The tetrahydrofuran was then removed *in vacuo*. The residue was diluted with water (25 mL) and extracted with ether (1 x 20 mL). The aqueous layer was acidified to pH = 2 with a 3N aqueous hydrochloric acid solution. The solution was extracted with methylene chloride (3 x 25 mL). The organics were washed with a saturated aqueous sodium chloride solution (2 x 25 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo* to give 3-cyclopentyl-2-(3-nitro-phenyl)-propionic acid (0.48 g, 91.9%) as a tan solid: mp 95-99°C; EI-HRMS m/e calcd for  $C_{14}H_{17}NO_4$  ( $M^+$ ) 263.1157, found 263.1156.

15

- A solution of 3-cyclopentyl-2-(3-nitro-phenyl)-propionic acid (432 mg, 1.64 mmol) in methylene chloride (16 mL) was cooled to 0°C and then treated with a 2.0M solution of oxalyl chloride in methylene chloride (0.90 mL, 1.80 mmol) and a few drops of *N,N*-dimethylformamide. The reaction mixture was stirred at 0°C for 15 min and at 25°C for 20 1.2 h. The reaction mixture was then treated with a solution of 2-aminothiazole (361.4 mg, 3.61 mmol) and *N,N*-diisopropylethylamine (0.70 mL, 3.93 mmol) in tetrahydrofuran (16 mL). The reaction mixture was stirred at 25°C for 6 h. At this time, the reaction was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh 70/30 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(nitrophenyl)-N-thiazol-2-yl-propionamide (409.3 mg, 72.2%) as a tan solid: mp 171-174°C; EI-HRMS m/e calcd for  $C_{17}H_{19}N_3O_3S$  ( $M^+$ ) 345.1147, found 345.1153.

25

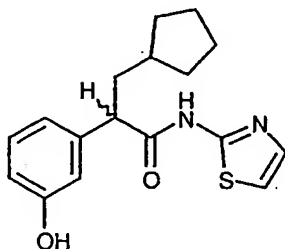


of chloroform/methanol (9:1). The organics were dried over sodium sulfate, filtered, and concentrated in vacuo. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 70/30 hexanes/ethyl acetate with glacial acetic acid) afforded 3-cyclopentyl-2-(3-methoxy-phenyl)-propionic acid (1.05 g, 79.8%) as a clear wax: EI-HRMS m/e calcd for  $C_{15}H_{20}O_3$  ( $M^+$ ) 248.1412, found 248.1409.

A solution of 3-cyclopentyl-2-(3-methoxy-phenyl)-propionic acid (500 mg, 2.0 mmol) in methylene chloride (20 mL) cooled to 0°C was treated with a 2.0M solution of oxalyl chloride in methylene chloride (1.1 mL, 2.20 mmol) and a few drops of *N,N*-dimethylformamide. The reaction mixture was stirred at 0°C for 10 min then at 25°C for 30 min. The reaction mixture was then treated with 2-aminothiazole (444 mg, 4.42 mmol) and *N,N*-diisopropylethylamine (0.84 mL, 4.83 mmol) in tetrahydrofuran (10.1 mL). This solution was stirred at 25°C for 18 h. At this time, the reaction was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 80/20 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(3-methoxy-phenyl)-*N*-thiazol-2-yl-propionamide (549mg, 82.6%) as a white solid: mp 44-45°C; EI-HRMS m/e calcd for  $C_{18}H_{22}N_2O_2S$  ( $M^+$ ) 330.1402 found 330.1398.

### Example 113

#### 3-Cyclopentyl-2-(3-hydroxy-phenyl)-*N*-thiazol-2-yl-propionamide



A 1.0M solution of boron tribromide in methylene chloride (3.53 mL, 3.53 mmol) at 25°C was treated with a solution of 3-cyclopentyl-2-(3-methoxy-phenyl)-*N*-thiazol-2-yl-propionamide (prepared in Example 112, 0.11 g, 0.35 mmol) in methylene chloride (3.5

sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-trifluoromethoxy-phenyl)-propionic acid (0.31 g, 30.6%) as a tan solid: mp 62-64°C; EI-HRMS *m/e* calcd for  $C_{15}H_{17}F_3O_3$  ( $M^+$ ) 302.1129 found 302.1131.

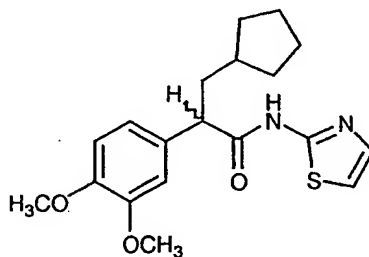
5

A solution of 3-cyclopentyl-2-(4-trifluoromethoxy-phenyl)-propionic acid (0.16 g, 0.52 mmol) in methylene chloride (5.3 mL) cooled to 0°C was treated with a 2.0M solution of oxalyl chloride in methylene chloride (0.29 mL, 0.58 mmol) and a few drops of *N,N*-dimethylformamide. The reaction mixture was stirred at 0°C for 10 min and at 25°C for 10 30 min. The reaction mixture was then treated with a solution of 2-aminothiazole (0.11 g, 1.16 mmol) and *N,N*-diisopropylethylamine (0.22 mL, 1.27 mmol) in tetrahydrofuran (2.65 mL). The reaction mixture was stirred at 25°C for 18 h. At this time, the reaction was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh 80/20 hexanes/ethyl acetate) afforded 3-cyclopentyl-*N*-thiazol-2-yl-2-(4-trifluoromethoxy-phenyl)-propionamide (203.8 mg, 100%) as a white solid: mp 168-170°C; EI-HRMS *m/e* calcd for  $C_{18}H_{19}F_3N_2O_2S$  ( $M^+$ ) 384.1119, found 384.1118.

15

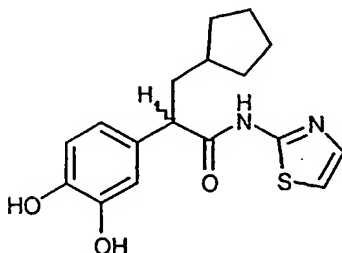
### Example 115

#### 3-Cyclopentyl-2-(3,4-dimethoxy-phenyl)-*N*-thiazol-2-yl-propionamide



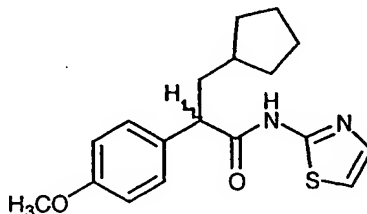
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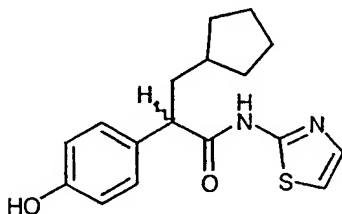
A solution of freshly prepared lithium diisopropylamide (58.5 mL of a 0.91M stock solution, 53.2 mmol) cooled to -78°C was treated with (3,4-dimethoxy-phenyl)-acetic acid (4.97 g, 25.3 mmol) in tetrahydrofuran/1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-

**Example 116****3-Cyclopentyl-2-(3,4-dihydroxy-phenyl)-N-thiazol-2-yl-propionamide**

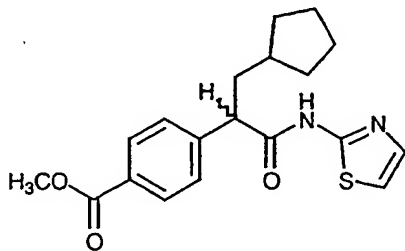
5 A 1.0M solution of boron tribromide in methylene chloride (7.43 mL, 7.43 mmol) at 25°C was treated with a solution of 3-cyclopentyl-2-(3,4-dimethoxy-phenyl)-N-thiazol-2-yl-propionamide (prepared in Example 115, 0.27 g, 0.74 mmol) in methylene chloride (7.43 mL). This solution was stirred at 25°C for 1 h. At this time, the reaction was cooled to 0°C and treated with a dilute aqueous ammonium hydroxide solution. This mixture was stirred at 0°C for 20 min. At this time, the reaction was poured into water and was extracted with chloroform (3 x 50 mL). The organics were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 70/30 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(3,4-dihydroxy-phenyl)-N-thiazol-2-yl-propionamide (38.8 mg, 15.7%) as a white solid; mp 170-173°C; EI-HRMS m/e calcd for C<sub>17</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub>S (M<sup>+</sup>) 332.1194 found 332.1192.

15

**Example 117****3-Cyclopentyl-2-(4-methoxy-phenyl)-N-thiazol-2-yl-propionamide**

**Example 118****3-Cyclopentyl-2-(4-hydroxy-phenyl)-N-thiazol-2-yl-propionamide**

- 5 A solution 3-cyclopentyl-2-(4-methoxy-phenyl)-N-thiazol-2-yl-propionamide (1.03 g, 3.12 mmol) in methylene chloride (31.26 mL) at 25°C was treated with a 1.0M solution of boron tribromide in methylene chloride (31.26 mL, 31.26 mmol). This solution was stirred at 25°C for 4 h. At this time, the reaction was cooled to 0°C and was then quenched by the dropwise addition of a dilute aqueous ammonium hydroxide solution.
- 10 The resulting solution was stirred at 0°C for 15 min. This mixture was then poured into water (50 mL) and extracted with ethyl acetate (3 x 30 mL). The organics were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 70/30 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-hydroxy-phenyl)-N-thiazol-2-yl-propionamide (626.8 mg, 63.4%) as a off-white solid: mp 198-
- 15 200°C; EI-HRMS *m/e* calcd for C<sub>17</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>S (M<sup>+</sup>) 316.1245 found 316.1256.

**Example 119****4-[2-Cyclopentyl-1-(thiazol-2-ylcarbonyl)-ethyl]-benzoic acid methyl ester**

acid (70 mg, 11.7%) as a white solid: mp 235-237°C; EI-HRMS m/e calcd for  $C_9H_8O_4$  ( $M^+$ ) 180.0422, found 180.

5 A mixture of 4-carboxymethyl-benzoic acid (0.20 g, 1.11 mmol) and nickel(II) chloride hexahydrate (27 mg, 0.11 mol) in methanol (1.11 mL) was heated at 120°C for 24 h. At this time, the reaction mixture was cooled to 25°C and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 70/30 hexanes/ethyl acetate) afforded 4-methoxycarbonylmethyl-benzoic acid methyl ester (66.7 mg, 28.8%) as a clear oil: EI-HRMS m/e calcd for  $C_{11}H_{12}O_4$  ( $M^+$ ) 208.0735, found 208.0733.

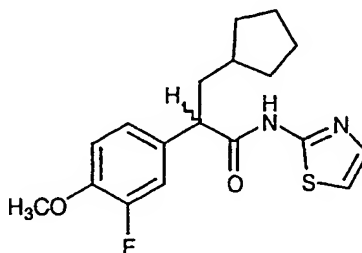
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A solution of freshly prepared lithium diisopropylamide (2.3 mL of a 0.31M stock solution, 0.71mmol) cooled to -78°C was treated with a solution of 4-methoxycarbonylmethyl-benzoic acid methyl ester (66 mg, 0.31 mmol) in tetrahydrofuran/1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (0.85 mL, 3:1).  
15 The resulting solution was stirred at -78°C for 45 min. At this time, the reaction was treated with a solution of iodomethylcyclopentane (86 mg, 0.40 mmol) in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (1 mL). The reaction mixture was stirred at -78°C for 4 h. The reaction was then warmed to 25°C and stirred at 25°C for 18 h. At this time, the reaction mixture was quenched by the slow addition of a saturated aqueous  
20 ammonium chloride solution (10 mL). The reaction mixture was then poured into water (50 mL). This solution was extracted into ethyl acetate (3 x 25 mL). The organics were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 80/20 hexanes/ethyl acetate) afforded 4-(2-cyclopentyl-1-methoxycarbonyl-ethyl)-benzoic acid methyl ester (60.5 mg, 65.7%) as a  
25 clear oil: EI-HRMS m/e calcd for  $C_{17}H_{22}O_4$  ( $M^+$ ) 290.1518, found 290.1518.

A solution of 4-(2-cyclopentyl-1-methoxycarbonyl-ethyl)-benzoic acid methyl ester (0.40 g, 1.37 mmol) in tetrahydrofuran/water/methanol (13.7 mL, 3:1:1) was treated with a 1N

## Example 120

## 3-Cyclopentyl-2-(3-fluoro-4-methoxy-phenyl)-N-thiazol-2-yl-propionamide



5 A solution of (3-fluoro-4-hydroxy-phenyl)-acetic acid (1.0 g, 5.87 mmol) in methanol (20 mL) was treated with a catalytic amount of sulfuric acid. The reaction was heated at 120°C for 6 h. At this time, the reaction was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate) afforded (3-fluoro-4-hydroxy-phenyl)-acetic acid methyl ester (1.05 g, 97.6%) as a white solid: mp 34-36°C: EI-HRMS *m/e* calcd for C<sub>9</sub>H<sub>9</sub>FO<sub>3</sub> (M<sup>+</sup>) 184.0535, found 184.0533.

10

A mixture of 3-fluoro-4-hydroxy-phenyl)-acetic acid methyl ester (1.0 g, 5.43 mmol), potassium carbonate (1.87 g, 13.57 mmol), and methyl iodide (1.12 g, 8.14 mmol) in acetone (27.1 mL) was heated at 90°C for 4 h. At this time, the potassium carbonate was removed by filtration. The filtrate was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 80/20 hexanes/ethyl acetate) afforded (3-fluoro-4-methoxy-phenyl)-acetic acid methyl ester (1.01 g, 94.3%) as a clear oil: EI-HRMS *m/e* calcd for C<sub>10</sub>H<sub>11</sub>FO<sub>3</sub> (M<sup>+</sup>) 198.0692, found 198.0693.

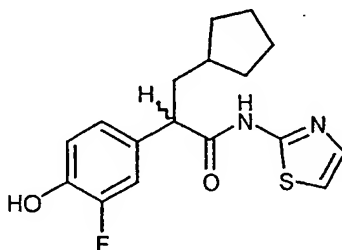
20 A solution of freshly prepared lithium diisopropylamide (21.6 mL of 0.31M stock solution, 6.69 mmol) cooled to -78°C was treated with a solution of (3-fluoro-4-methoxy-phenyl)-acetic acid methyl ester (1.26 g, 6.38 mmol) in tetrahydrofuran/1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (16 mL, 3:1). The resulting solution was stirred at -78°C for 45 min. At this time, the reaction was treated with a solution of iodomethylcyclopentane (1.47 g, 7.02 mmol) in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-

time, the reaction was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 80/20 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(3-fluoro-4-methoxy-phenyl)-N-thiazol-2-yl-propionamide (538.4 mg, 100%) as a white solid: mp 51-53°C: EI-HRMS *m/e* calcd for  $C_{18}H_{21}FN_2O_2S$  ( $M^+$ ) 348.1307 found 348.1312.

5

### Example 121

#### 3-Cyclopentyl-2-(3-fluoro-4-hydroxy-phenyl)-N-thiazol-2-yl-propionamide



A solution of 3-cyclopentyl-2-(3-fluoro-4-methoxy-phenyl)-N-thiazol-2-yl-propionamide (prepared in Example 120, 305.4 mg, 0.87 mmol) in methylene chloride (8.7 mL) at 25°C was treated with a 1.0M solution of boron tribromide in methylene chloride (8.75 mL, 8.75 mmol). This solution was stirred at 25°C for 5 h. At this time, the reaction was cooled to 0°C and quenched by the dropwise addition of a dilute aqueous ammonium hydroxide solution. The resulting solution was stirred at 0°C for 15 min. This mixture was then poured into water (50 mL) and extracted with ethyl acetate (3 x 30 mL). The organics were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(3-fluoro-4-hydroxy-phenyl)-N-thiazol-2-yl-propionamide (212.7 mg, 72.5%) as a white solid: mp 199-201°C: EI-HRMS *m/e* calcd for  $C_{17}H_{19}FN_2O_2S$  ( $M^+$ ) 334.1151 found 334.1152.

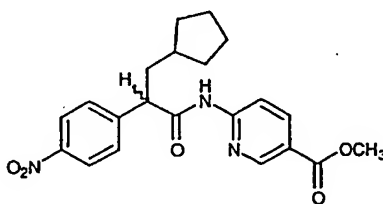
stirred at 25°C for 18 h. At this time, the reaction was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230–400 mesh, 50/50 hexanes/ethyl acetate) afforded 6-[2-(3-chloro-phenyl)-3-cyclopentyl-propionylamino]-nicotinic acid methyl ester (151.9 mg, 19.7%) as a colorless oil: EI-HRMS *m/e* calcd for  $C_{21}H_{23}ClN_2O_3$  ( $M^+$ ) 386.1397, found 386.1398.

A solution of 6-[2-(3-chloro-phenyl)-3-cyclopentyl-propionylamino]-nicotinic acid methyl ester (146.9 mg, 0.38 mmol) in tetrahydrofuran/water/methanol (10 mL, 3:1:1) at 25°C was treated with a 2N aqueous sodium hydroxide solution (0.4 mL, 0.80 mmol). The reaction mixture was stirred at 25°C for 4 d. At this time, the reaction was concentrated *in vacuo*. The residue was diluted with water (50 mL) and extracted with diethyl ether (1 x 50 mL). The aqueous layer was acidified to pH = 1 by the dropwise addition of a 3N aqueous hydrochloric acid solution. This solution was extracted with a solution of methylene chloride/methanol (3:1, 3 x 75 mL). The organics were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The resulting solid was triturated with diethyl ether/hexanes (2:1) to afford 6-[2-(3-chloro-phenyl)-3-cyclopentyl-propionylamino]-nicotinic acid (63.6 mg, 44.4%) as a white solid: mp 251–255°C; EI-HRMS *m/e* calcd for  $C_{20}H_{21}ClN_2O_3$  ( $M^+$ ) 372.1240, found 372.1250.

20

### Example 123

#### 6-[3-Cyclopentyl-2-(4-nitro-phenyl)-propionylamino]-nicotinic acid methyl ester



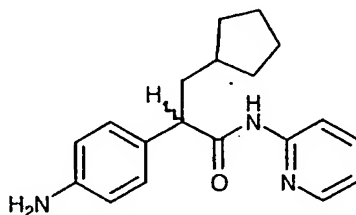
A solution of freshly prepared lithium diisopropylamide (430.55 mL of a 0.3M stock solution, 129.16 mmol) cooled to -78°C was treated with (4-nitro-phenyl)-acetic acid ethyl ester (26.32 g, 125.83 mmol) in tetrahydrofuran/hexamethylphosphoramide (312.5



methyl ester (532 mg, 3.5 mmol) in tetrahydrofuran (10 mL) and *N,N*-diisopropylethylamine (0.84 mL, 4.8 mmol). This solution was stirred at 25°C for 48 h. At this time, the reaction was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 80/20 hexanes/ethyl acetate) afforded 6-[3-cyclopentyl-2-(4-nitro-phenyl)-propionylamino]-nicotinic acid methyl ester (353.9 mg, 44.6%) as a pale orange glass: EI-HRMS *m/e* calcd for  $C_{21}H_{23}N_3O_5$  ( $M^+$ ) 397.1637, found 397.1631.

### Example 124

#### 2-(4-Amino-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide



A solution of 3-cyclopentyl-2-(4-nitro-phenyl)-propionic acid (prepared in Example 22, 263 mg, 1.0 mmol) in methylene chloride (10 mL) cooled to 0°C was treated with a 2.0M solution of oxalyl chloride in methylene chloride (0.6 mL, 1.2 mmol) and a few drops of *N,N*-dimethylformamide. The reaction mixture was stirred at 0°C for 15 min and at 25°C for 30 min. The reaction mixture was then treated with a solution of 2-aminopyridine (200.6 mg, 2.14 mmol) in tetrahydrofuran (5 mL) and *N,N*-diisopropylethylamine (0.42 mL, 2.4 mmol). This solution was stirred at 25°C for 48 h. At this time, the reaction was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 80/20 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-nitro-phenyl)-N-pyridin-2-yl-propionamide (138.6 mg, 40.9%) as a pale yellow glass: EI-HRMS *m/e* calcd for  $C_{19}H_{21}N_3O_3$  ( $M^+$ ) 339.1581, found 339.1582.

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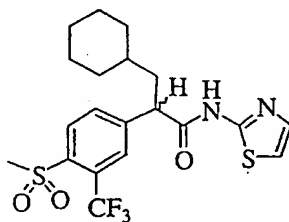
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A mixture of 3-cyclopentyl-2-(4-nitro-phenyl)-N-pyridin-2-yl-propionamide (130 mg, 0.38 mmol) in ethyl acetate (50 mL) and methanol (5 mL) was treated with a catalytic

under 60 psi of hydrogen gas in a Parr apparatus for 24 h. At this time, the catalyst was removed by filtration through a plug of celite. The filtrate was concentrated *in vacuo* to afford 6-[2-(4-amino-phenyl)-3-cyclopentyl-propionylamino]-nicotinic acid methyl ester (262.8 mg, 94.7%) as a pale yellow glass: EI-HRMS *m/e* calcd for  $C_{21}H_{25}N_3O_3$  ( $M^+$ ) 367.1895, found 367.1899.

### Example 126

#### 3-Cyclohexyl-2-(4-methanesulfonyl-3-trifluoromethyl-phenyl)-N-thiazol-2-yl-propionamide



10

A solution of isoamyl nitrite (4.02 mL, 30 mmol) in dimethyl disulfide (19.8 mL, 220 mmol) at 25°C was slowly treated with 4-bromo-2-(trifluoromethyl)aniline (4.8 g, 20 mmol). The reaction was exothermic with gas evolution. The resulting brown reaction mixture was heated to 80-90°C for 2 h, at which time, thin layer chromatography analysis of the reaction mixture indicated the absence of starting material. The reaction mixture was cooled to 25°C and then concentrated *in vacuo*. The resulting residue was dissolved in ethyl acetate (200 mL). The organic layer was washed successively with a 1N aqueous hydrochloric acid solution (1 x 200 mL) and a saturated aqueous sodium chloride solution (1 x 200 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Biotage chromatography (FLASH 40M, Silica, 8/1 hexanes/ethyl acetate) afforded 4-bromo-1-methylsulfonyl-2-trifluoromethyl-benzene (4.73 g, 87%) as a brown oil: EI-HRMS *m/e* calcd for  $C_8H_6BrF_3S$  ( $M^+$ ) 269.9326, found 269.9327.

20

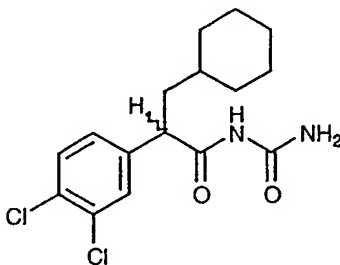
trifluoromethyl-benzene (2.12 g, 7 mmol) and the freshly prepared zinc compound in tetrahydrofuran. The resulting brick red solution was heated at 40-45°C for 2 d. The reaction mixture was cooled to 25°C and then poured into a saturated aqueous ammonium chloride solution (100 mL), and the organic compound was extracted into ethyl acetate (3  
5 x 75 mL). The combined organic extracts were washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Biotage chromatography (FLASH 40M, Silica, 9/1 to 3/1 hexanes/ethyl acetate) afforded (E)-3-cyclohexyl-2-(4-methanesulfonyl-3-trifluoromethyl-phenyl)-acrylic acid methyl ester (2.7 g, 99%) as a viscous oil: EI-HRMS *m/e* calcd for  
10  $C_{18}H_{21}F_3O_4S$  ( $M^+$ ) 391.1191, found 391.1200.

A solution of nickel(II) chloride hexahydrate (36.6 mg, 0.154 mmol) and (E)-3-cyclohexyl-2-(4-methanesulfonyl-3-trifluoromethyl-phenyl)-acrylic acid methyl ester (302 mg, 0.77 mmol) in methanol (8 mL) was cooled to 0°C and then treated with sodium  
15 borohydride (87 mg, 2.29 mmol) in four portions. After the addition, the black reaction mixture was stirred for 15 min at 0°C and then allowed to warm to 25°C where it was stirred for 15 h. The black solid was filtered using filter paper and washed with methanol. The combined solvents were concentrated *in vacuo*, and the residue was diluted with ethyl acetate (50 mL). The organic layer was washed successively with a 3N  
20 aqueous hydrochloric acid solution (1 x 50 mL), a saturated aqueous sodium bicarbonate solution (1 x 50 mL) and a saturated aqueous sodium chloride solution (1 x 50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to afford racemic 3-cyclohexyl-2-(4-methanesulfonyl-3-trifluoromethyl-phenyl)-propionic acid methyl ester (280 mg, 93%) as a viscous oil: EI-HRMS *m/e* calcd for  $C_{18}H_{23}F_3O_4S$  ( $M^+$ ) 392.1269,  
25 found 392.1276.

A solution of 3-cyclohexyl-2-(4-methanesulfonyl-3-trifluoromethyl-phenyl)-propionic acid methyl ester (265 mg, 0.67 mmol) in ethanol (5 mL) was treated with a 1N aqueous sodium hydroxide solution (1.5 mL). The solution was heated at 45-50°C for 5 h, at

## Example 127

## (A) 3-Cyclohexyl-2-(3,4-dichloro-phenyl)-propionyl]-urea



- 5 A solution of (3,4-dichloro-phenyl)-acetic acid (14.0 g, 0.068 mol) in methanol (71mL) was treated with a catalytic amount of sulfuric acid. The reaction mixture was refluxed for 12 h. The reaction was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate) afforded (3,4-dichloro-phenyl)-acetic acid methyl ester (15.0 g, quant.) as a white solid: mp 30-32°C; EI-HRMS *m/e* calcd for C<sub>9</sub>H<sub>8</sub>Cl<sub>2</sub>O<sub>2</sub> (M<sup>+</sup>) 217.9901, found 217.9907.
- 10

- A solution of freshly prepared lithium diisopropylamide (16.3 mL of a 0.31M stock solution, 5.04 mmol) cooled to -78°C was treated with (3,4-dichloro-phenyl)-acetic acid methyl ester (1.0 g, 4.58 mmol) in tetrahydrofuran/hexamethylphosphoramide (8.6 mL, 3:1). The resulting solution was stirred at -78°C for 45 min. At this time, the reaction was treated with a solution of bromomethylcyclohexane (1.92 mL, 13.76 mmol) in hexamethylphosphoramide (1 mL). The reaction mixture was stirred at -78°C for 3 h. The reaction was warmed to 25°C and stirred at 25°C for 16 h. The reaction mixture was then quenched by the dropwise addition of a saturated aqueous ammonium chloride solution (20 mL). This mixture was poured into water (100 mL) and extracted with ethyl acetate (3 x 50 mL). The organics were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 75/25 hexanes/ethyl acetate) afforded 3-cyclohexyl-2-(3,4-dichloro-phenyl)-propionic acid
- 15
- 20

(f) From 3-cyclohexyl-2-(3,4-dichloro-phenyl)-propionic acid methyl ester and methyl urea: [3-Cyclohexyl-2-(3,4-dichloro-phenyl)-propionyl]-3-methyl-urea as a white solid: mp 69-73°C; EI-HRMS m/e calcd for  $C_{17}H_{22}Cl_2N_2O_2$  ( $M^+$ ) 356.1058, found 356.1046.

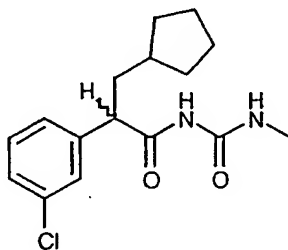
(g) From 1-[2-(3,4-dichloro-phenyl)-4-methyl-pentanoyl]-3-methyl ester and methyl-urea:  
5 1-[2-(3,4-Dichloro-phenyl)-4-methyl-pentanoyl]-3-methyl-urea as a white solid: mp 123-125°C; EI-HRMS m/e calcd for  $C_{14}H_{18}Cl_2N_2O_2$  ( $M^+$ ) 316.0745, found 316.0740.

(h) From 2-(3,4-dichloro-phenyl)-hexanoic acid methyl ester and methyl-urea: 1-[2-(3,4-Dichloro-phenyl)-hexanoyl]-3-methyl-urea as a clear oil: EI-HRMS m/e calcd for  $C_{14}H_{18}Cl_2N_2O_2$  ( $M^+$ ) 316.0743, found 316.0745.

10

### Example 128

#### 1-[2-(3-Chloro-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea



(3-Chloro-phenyl)-acetic acid (6.03 g, 0.03 mol) was dissolved in ethanol (37.7 mL) and  
15 treated with a catalytic amount of sulfuric acid. The reaction mixture was refluxed for 12 h. The reaction was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate) afforded (3-chloro-phenyl)-acetic acid ethyl ester (6.10 g, 86.8%) as a clear oil: EI-HRMS m/e calcd for  $C_{10}H_{11}ClO_2$  ( $M^+$ ) 198.0448, found 198.0442.

20

A solution of freshly prepared lithium diisopropylamide (23 mL of 0.31M stock solution, 7.13 mmol) cooled to -78°C was treated with (3-chloro-phenyl)-acetic acid ethyl ester (1.28 g, 6.48 mmol) in tetrahydrofuran/hexamethylphosphoramide (16.1 mL, 3:1). The

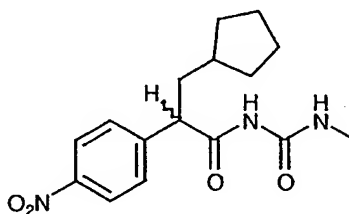
A solution of (3,4-difluoro-phenyl)-acetic acid (5.0 g, 0.029 mol) in methanol (30.0 mL) was treated with a catalytic amount of sulfuric acid. The reaction mixture was refluxed for 4 h. The reaction was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate) afforded (3,4-difluoro-phenyl)-acetic acid methyl ester (5.15 g, 95.2%) as a clear oil: EI-HRMS *m/e* calcd for  $C_9H_8F_2O_2$  ( $M^+$ ) 186.0493, found 186.0492.

A solution of freshly prepared lithium diisopropylamide (23.0 mL of a 0.31M stock solution, 7.13 mmol) cooled to  $-78^\circ\text{C}$  was treated with (3,4-difluoro-phenyl)-acetic acid methyl ester (1.20 g, 6.48 mmol) in tetrahydrofuran/hexamethylphosphoramide (16.1 mL, 3:1). The resulting solution was stirred at  $-78^\circ\text{C}$  for 45 min. At this time, the reaction was treated with a solution of iodomethylcyclopentane (1.50 g, 7.13 mmol) in hexamethylphosphoramide (1 mL). The reaction mixture was stirred at  $-78^\circ\text{C}$  for 4 h. The reaction was then warmed to  $25^\circ\text{C}$  and was stirred at  $25^\circ\text{C}$  for 16 h. The reaction mixture was then quenched by the dropwise addition of a saturated aqueous ammonium chloride solution (20 mL). This mixture was poured into water (100 mL) and extracted with ethyl acetate (3 x 50 mL). The organics were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 75/25 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(3,4-difluoro-phenyl)-propionic acid methyl ester (1.79 g, quant.) as a clear oil: EI-HRMS *m/e* calcd for  $C_{15}H_{18}F_2O_2$  ( $M^+$ ) 268.1275, found 268.1278.

A mixture of 3-cyclopentyl-2-(3,4-difluoro-phenyl)-propionic acid methyl ester (1.65 g, 6.14 mmol) and methyl urea (683 mg, 9.22 mmol) in a solution of magnesium methoxide in methanol (7.4 wt%, 16.6 mL, 12.3 mmol) was refluxed at  $100^\circ\text{C}$  for 8 h. The reaction mixture was then concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 75/25 hexanes/ethyl acetate) afforded 1-[3-cyclopentyl-2-(3,4-difluoro-phenyl)-propionyl]-3-methyl-urea (180 mg, 9.4%) as a white solid: mp  $111-113^\circ\text{C}$ ; EI-HRMS *m/e* calcd for  $C_{16}H_{20}F_2N_2O_2$  ( $M^+$ ) 310.1493, found 310.1499.

A mixture of 2-(4-chloro-phenyl)-3-cyclopentyl-propionic acid ethyl ester (1.65 g, 5.89 mmol) and methyl urea (654 mg, 8.83 mmol) in a solution of magnesium methoxide in methanol (7.4 wt%, 16.9 mL, 11.78 mmol) was refluxed at 100°C for 6 h. The reaction mixture was then concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 75/25 hexanes/ethyl acetate) afforded 1-[2-(4-chloro-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea (105.3 mg, 5.8 %) as a white solid: mp 145-147°C; EI-HRMS *m/e* calcd for C<sub>16</sub>H<sub>21</sub>ClN<sub>2</sub>O<sub>2</sub> (M<sup>+</sup>) 308.1292, found 308.1291.

10

**Example 131****1-[3-Cyclopentyl-2-(4-nitro-phenyl)-propionyl]-3-methyl-urea**

A solution of freshly prepared lithium diisopropylamide (430.55 mL of a 0.3M stock solution, 129.16 mmol) cooled to -78°C was treated with (4-nitro-phenyl)-acetic acid ethyl ester (26.32 g, 125.83 mmol) in tetrahydrofuran/hexamethylphosphoramide (312.5 mL, 3:1). The resulting solution was stirred at -78°C for 45 min. At this time, the reaction was treated with a solution of iodomethylcyclopentane (27.75 g, 132.1 mmol) in hexamethylphosphoramide (27.8 mL). The mixture was stirred at -78°C for 4 h. The reaction was then warmed to 25°C and was stirred at 25°C for 16 h. The reaction mixture was then quenched by the dropwise addition of a saturated aqueous ammonium chloride solution (250 mL). The reaction mixture was concentrated *in vacuo*. The residue was diluted with water (250 mL) and extracted with ethyl acetate (3 x 300 mL). The organics were washed with a saturated aqueous lithium chloride solution (2 x 250 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 95/5 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-

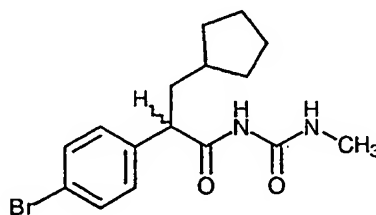
lithium chloride solution (2 x 50 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 95/5 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-phenyl-propionic acid ethyl ester (1.70 g, quant.) as a pale yellow oil: EI-HRMS *m/e* calcd for  $C_{16}H_{22}O_2$  ( $M^+$ ) 247.1698, found 247.1704.

A mixture of 3-cyclopentyl-2-phenyl-propionic acid ethyl ester (1.70 g, 7.06 mmol) and methyl urea (1.04 mg, 14.13 mmol) in a solution of magnesium methoxide in methanol (7.4 wt%, 130.3 mL, 21.18 mmol) was refluxed at 100°C for 24 h. The reaction mixture was then concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate) afforded 1-(3-cyclopentyl-2-phenyl-propionyl)-3-methyl-urea (1.21 mg, 62.4 %) as a white solid: mp 145-147°C; EI-HRMS *m/e* calcd for  $C_{16}H_{22}N_2O_2$  ( $M^+$ ) 274.1681, found 274.1682.

15

### Example 133

#### 1-[2-(4-Bromo-phenyl)-3-cyclopentyl-propionyl]-3-methyl urea



A solution of diisopropylamine (7.7 mL, 54.88 mmol) in dry tetrahydrofuran (23 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (10 mL) was cooled to -78°C under nitrogen and then treated with a 2.5M solution of *n*-butyllithium in hexanes (22.0 mL, 54.88 mmol). The reaction mixture was stirred at -78°C for 30 min and then treated dropwise with a solution of 4-bromophenylacetic acid (5.62 g, 26.13 mmol) in dry tetrahydrofuran (23 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (10 mL). The reaction mixture turned dark in color and was allowed to stir at -78°C for 1 h,

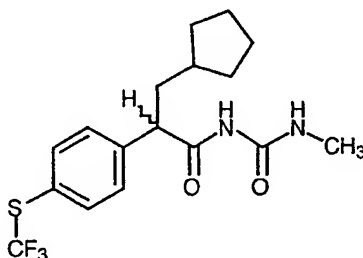


230 mesh, 3/1 hexanes/ethyl acetate) afforded 1-[2-(4-bromo-phenyl)-3-cyclopentyl-propionyl]-3-methyl urea (58.7 mg, 12%) as a white solid: mp 184-186°C; EI-HRMS m/e calcd for  $C_{16}H_{21}BrN_2O_2$  ( $M^+$ ) 352.0786, found 352.0791.

5

## Example 134

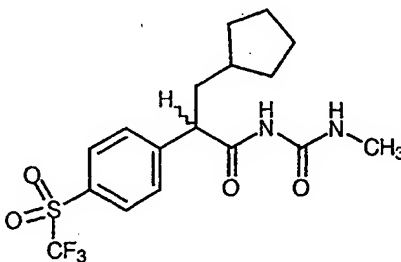
## 1-[3-Cyclopentyl-2-(4-trifluoromethylsulfanyl-phenyl)-propionyl]-3-methyl urea



A solution of diisopropylamine (2.4 mL, 16.80 mmol) in dry tetrahydrofuran (7.5 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (2.5 mL) was cooled to -78°C under nitrogen and then treated with a 2.5M solution of *n*-butyllithium in hexanes (6.7 mL, 16.80 mmol). The resulting reaction mixture was stirred at -78°C for 30 min and then treated dropwise with a solution of 4-(trifluoromethylthio)phenylacetic acid (1.89 g, 8.00 mmol) in dry tetrahydrofuran (7.5 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (2.5 mL). The reaction mixture was allowed to stir at -78°C for 55 min, at which time, a solution of iodomethylcyclopentane (1.85 g, 8.80 mmol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was allowed to warm to 25°C where it was stirred for 41 h. The reaction mixture was quenched with water and then concentrated *in vacuo* to remove tetrahydrofuran. The remaining aqueous phase was acidified to pH = 2 with a 10% aqueous hydrochloric acid solution and then extracted with ethyl acetate (1 x 300 mL). The organic layer was washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-trifluoromethylsulfanyl-

## Example 135

## 1-[3-Cyclopentyl-2-(4-trifluoromethanesulfonyl-phenyl)-propionyl]-3-methyl urea



A solution of diisopropylamine (2.4 mL, 16.80 mmol) in dry tetrahydrofuran (7.5 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (2.5 mL) was cooled to -78°C under nitrogen and then treated with a 2.5M solution of *n*-butyllithium in hexanes (6.7 mL, 16.80 mmol). The resulting reaction mixture was stirred at -78°C for 30 min and then treated dropwise with a solution of 4-(trifluoromethylthio)phenylacetic acid (1.89 g, 8.00 mmol) in dry tetrahydrofuran (7.5 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (2.5 mL). The reaction mixture was allowed to stir at -78°C for 55 min, at which time, a solution of iodomethylcyclopentane (1.85 g, 8.80 mmol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was allowed to warm to 25°C where it was stirred for 41 h. The reaction mixture was quenched with water and then concentrated *in vacuo* to remove tetrahydrofuran. The remaining aqueous phase was acidified to pH = 2 with a 10% aqueous hydrochloric acid solution and then extracted with ethyl acetate (1 x 300 mL). The organic layer was washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-trifluoromethylsulfonyl-phenyl)propionic acid (1.47 g, 58%) as a cream solid: mp 69-71°C; EI-HRMS *m/e* calcd for C<sub>15</sub>H<sub>17</sub>F<sub>3</sub>O<sub>2</sub>S (M<sup>+</sup>) 318.0901, found 318.0912.

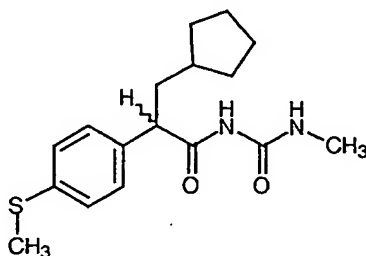
A solution of 3-cyclopentyl-2-(4-trifluoromethylsulfonyl-phenyl)propionic acid (1.33 g, 4.18 mmol) in methanol (10 mL) was treated slowly with 4 drops of concentrated sulfuric

mixture was then heated under reflux for 2 d. The reaction mixture was allowed to cool to 25°C and then filtered through celite. The celite was thoroughly washed with ethyl acetate until the solvent passing through the celite showed absence of desired product by thin layer chromatography. The filtrate was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/1 hexanes/ethyl acetate) afforded 1-[3-cyclopentyl-2-(4-trifluoromethanesulfonyl-phenyl)-propionyl]-3-methyl urea (119.3 mg, 28%) as a white solid: mp 191-192°C; FAB-HRMS *m/e* calcd for C<sub>17</sub>H<sub>21</sub>F<sub>3</sub>N<sub>2</sub>O<sub>4</sub>S (M+H)<sup>+</sup> 407.1252, found 407.1247.

10

## Example 136

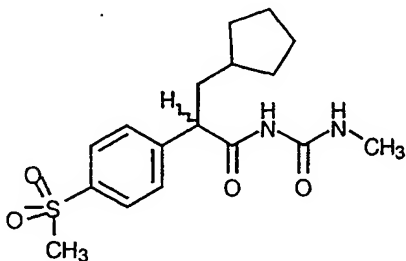
## 1-[3-Cyclopentyl-2-(4-methylsulfanyl-phenyl)-propionyl]-3-methyl urea



A solution of diisopropylamine (3.2 mL, 23.16 mmol) in dry tetrahydrofuran (10.3 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (3.4 mL) was cooled to -78°C under nitrogen and then treated with a 10M solution of *n*-butyllithium in hexanes (2.3 mL, 23.16 mmol). The resulting reaction mixture was stirred at -78°C for 30 min and then treated dropwise with a solution of 4-(methylthio)phenylacetic acid (2.01 g, 11.03 mmol) in dry tetrahydrofuran (10.3 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (3.4 mL). The reaction mixture was allowed to stir at -78°C for 1 h, at which time, a solution of iodomethylcyclopentane (2.55 g, 12.13 mmol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was stirred at -78°C for 30 min and then allowed to warm to 25°C where it was stirred for 24 h. The reaction mixture was quenched with water and then concentrated *in vacuo* to remove tetrahydrofuran. The remaining aqueous phase was acidified to pH = 2 with a 10%

## Example 137

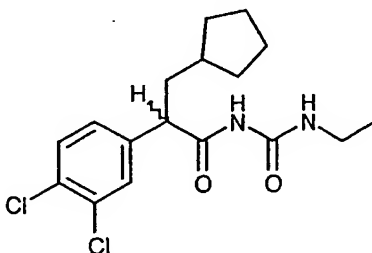
## 1-[3-Cyclopentyl-2-(4-methanesulfonyl-phenyl)-propionyl]-3-methyl urea



- 5 A solution of diisopropylamine (3.3 mL, 23.5 mmol) in dry tetrahydrofuran (50 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (10 mL) was cooled to -78°C under nitrogen and then treated with a 10M solution of *n*-butyllithium in hexanes (2.35 mL, 23.5 mmol). The yellow reaction mixture was stirred at -78°C for 30 min and then treated dropwise with a solution of 4-methylsulfonylphenylacetic acid (2.40 g, 11.2
- 10 mmol) in a small amount of dry tetrahydrofuran. After approximately one-half of the 4-methylsulfonylphenylacetic acid in dry tetrahydrofuran was added, a precipitate formed. Upon further addition of the remaining 4-methylsulfonylphenylacetic acid in dry tetrahydrofuran, the reaction mixture became thick in nature. After complete addition of the 4-methylsulfonylphenylacetic acid in dry tetrahydrofuran, the reaction mixture was
- 15 very thick and became difficult to stir. An additional amount of dry tetrahydrofuran (20 mL) was added to the thick reaction mixture, and the reaction mixture was stirred at -78°C for 45 min, at which time, a solution of iodomethylcyclopentane (2.35 g, 11.2 mmol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was allowed to warm to 25°C where it was stirred for 15 h. The reaction mixture
- 20 was quenched with water (100 mL), and the resulting yellow reaction mixture was concentrated *in vacuo* to remove tetrahydrofuran. The aqueous residue was acidified to pH = 2 using concentrated hydrochloric acid. The aqueous layer was extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/3 hexanes/ethyl

## Example 138

## (A) 1-[3-Cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-ethyl-urea



A solution of triphenylphosphine (28.80 g, 109.8 mmol) and imidazole (14.9 g, 219.6  
5 mmol) in methylene chloride (160 mL) was cooled to 0°C and then slowly treated with  
iodine (27.87 g, 109.8 mmol). The reaction mixture was then treated dropwise with a  
solution of cyclopentylmethanol (10.0 g, 99.8 mmol) in methylene chloride (10 mL). The  
resulting reaction mixture was allowed to warm to 25°C, where it was stirred for 4 h. The  
reaction mixture was then diluted with water (50 mL), and the reaction mixture was  
10 further extracted with methylene chloride (3 x 20 mL). The combined organic layers  
were dried over sodium sulfate, filtered and concentrated *in vacuo* at 25°C. The resulting  
solid was washed with pentane (4 x 50 mL) and filtered through a silica gel plug. The  
filtrate was concentrated *in vacuo* at 25°C to afford iodomethylcyclopentane (18.48 g,  
88%) as a clear colorless liquid: EI-HRMS *m/e* calcd for C<sub>6</sub>H<sub>11</sub>I (M<sup>+</sup>) 209.9906, found  
15 209.9911.

A solution of diisopropylamine (13.36 mL, 101.89 mmol) in tetrahydrofuran (250 mL)  
was cooled to -78°C under a nitrogen atmosphere and then treated with a 2.0M solution  
of *n*-butyllithium in hexanes (51 mL, 101.89 mmol). The reaction mixture was stirred at -  
20 78°C for 15 min, at which time, a solution of 3,4-dichlorophenyl acetic acid (9.08 g, 44.3  
mmol) in tetrahydrofuran (60 mL) and hexamethylphosphoramide (20 mL) was slowly  
added via a cannula. The bright yellow solution was allowed to stir at -78°C for 1 h, at  
which time, a solution of iodomethylcyclopentane (11.17 g, 53.2 mmol) in  
hexamethylphosphoramide (10 mL) was added via a cannula. The reaction mixture was

afforded 1-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-ethyl-urea (29 mg, 26%) as a white foam: EI-HRMS m/e calcd for  $C_{17}H_{22}Cl_2N_2O_2$  ( $M^+$ ) 356.1058, found 356.1066.

5 (B) In an analogous manner, there were obtained:

(a) From 3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionamide and isopropyl isocyanate: 1-[3-Cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-isopropyl-urea as a white solid: mp 134.6-138.3°C; EI-HRMS m/e calcd for  $C_{18}H_{24}Cl_2N_2O_2$  ( $M^+$ ) 370.1215, found 370.1232.

10 (b) From 3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionamide and propyl isocyanate: 1-[3-Cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-propyl-urea as a white solid: mp 117.8-120°C; EI-HRMS m/e calcd for  $C_{18}H_{24}Cl_2N_2O_2$  ( $M^+$ ) 370.1215, found 370.1209.

(c) From 3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionamide and ethyl 3-isocyanatopropionate: 3-{3-[3-Cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido}-  
15 propionic acid ethyl ester as a light yellow oil: EI-HRMS m/e calcd for  $C_{20}H_{26}Cl_2N_2O_4$  ( $M^+$ ) 428.1270, found 428.1265.

(d) From 3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionamide and ethyl isocyanatoacetate: {3-[3-Cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido}-acetic  
acid ethyl ester as a light yellow oil: EI-HRMS m/e calcd for  $C_{19}H_{24}Cl_2N_2O_4$  ( $M^+$ )  
20 414.1113, found 414.1108.

(e) From 3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionamide and allyl isocyanate: 1-Allyl-3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-urea as a clear colorless oil: EI-HRMS m/e calcd for  $C_{18}H_{22}Cl_2N_2O_2$  ( $M^+$ ) 368.1058, found 368.1064.

74.6°C;  $[\alpha]_{589}^{23} = -27.6^\circ$  ( $c=0.188$ , chloroform); EI-HRMS  $m/e$  calcd for  $C_{20}H_{25}Cl_2NO_3$  ( $M^+$ ) 397.1211, found 397.1212.

A solution of 3-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionyl]-4(S)-isopropyl-oxazolidin-2-one (1.88 g, 4.72 mmol) in tetrahydrofuran (73 mL) and water (22 mL) cooled to 0°C was treated with a 30% aqueous hydrogen peroxide solution (2.1 mL) and lithium hydroxide (394 mg, 9.4 mmol). The reaction was stirred at 0°C for 1 h. At this time, the reaction was quenched with a saturated aqueous sodium sulfite solution (16 mL) followed by the addition of an aqueous solution of 0.5N sodium bicarbonate (50 mL). The tetrahydrofuran was then removed *in vacuo*. The residue was diluted with water (40 mL) and extracted with methylene chloride (3 x 20 mL). The aqueous layer was then acidified to pH = 2 with a 5N aqueous hydrochloric acid solution and extracted with ethyl acetate (4 x 25 mL). The ethyl acetate layers were then dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford 3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionic acid (928 mg, 70%) as a white solid; mp 75.1-78.3°C;  $[\alpha]_{589}^{23} = -50.3^\circ$  ( $c=0.100$ , chloroform); EI-HRMS  $m/e$  calcd for  $C_{14}H_{16}Cl_2O_2$  ( $M^+$ ) 286.0527, found 286.0535.

A solution of 3-cyclopentyl-2(R)-(3,4-dichlorophenyl)-propionic acid (105 mg, 0.37 mmol) in methylene chloride (10 mL) and 1 drop of *N,N*-dimethylformamide was cooled to 0°C and then treated with a 2.0M solution of oxalyl chloride in methylene chloride (0.18 mL, 0.37 mmol). The reaction was stirred for 30 min at 0°C, at which time, 1,1,1,3,3,3-hexamethyldisilazane (0.25 mL, 1.17 mmol) was added to the reaction mixture. The reaction was then allowed to slowly warm to 25°C and stirred at 25°C for 16h. The reaction mixture was then washed with a 5% aqueous sulfuric acid solution (2 x 10 mL). The combined aqueous layers were extracted with methylene chloride (3 x 10 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (1 x 10 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 60/40 hexanes/ethyl

89%) as a yellow oil: EI-HRMS *m/e* calcd for  $C_9H_8ClNO_4$  ( $M^+$ ) 229.0142, found 229.0146.

A solution of diisopropylamine (3.35 mL, 23.9 mmol) in dry tetrahydrofuran (45 mL) and  
5 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (15 mL) was cooled to  $-78^\circ\text{C}$  and  
then treated dropwise with a 2.5M solution of *n*-butyllithium in hexanes (9.56 mL, 23.9  
mmol) over a 10 min period. The pale yellow reaction mixture was stirred at  $-78^\circ\text{C}$  for  
20 min and then slowly treated with a solution of 4-chloro-3-nitrophenylacetic acid  
methyl ester (5.00 g, 21.8 mmol) in a small amount of tetrahydrofuran over a 15 min  
10 period. The reaction mixture turned deep purple (almost black) in color. The reaction  
mixture was then stirred at  $-78^\circ\text{C}$  for 1 h, at which time, a solution of  
iodomethylcyclopentane (4.58 g, 21.8 mol) in a small amount of dry tetrahydrofuran was  
added dropwise. The reaction mixture was then stirred at  $-78^\circ\text{C}$  and then allowed to  
warm to  $25^\circ\text{C}$ , where it was stirred for 48 h. The reaction mixture was quenched with a  
15 saturated aqueous ammonium chloride solution (50 mL), and the resulting reaction  
mixture was concentrated *in vacuo* to remove tetrahydrofuran. The remaining residue  
was diluted with ethyl acetate (150 mL) and water (50 mL). The organic phase was  
washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate,  
filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400  
20 mesh, 4/1 hexanes/ethyl acetate) afforded 2-(4-chloro-3-nitrophenyl)-3-cyclopentyl-  
propionic acid methyl ester (2.17 g, 32%) as a yellow oil: EI-HRMS *m/e* calcd for  
 $C_{15}H_{18}ClNO_4$  ( $M^+$ ) 311.0924, found 311.0927.

A solution of 2-(4-chloro-3-nitrophenyl)-3-cyclopentyl-propionic acid methyl ester (1.00  
25 g, 3.21 mmol) and sodium methanesulfinate (0.36 g, 3.53 mmol) in dimethyl sulfoxide (3  
mL) was heated at  $130^\circ\text{C}$  for 5 h. The black reaction mixture was then poured over ice  
(20 g), resulting in the formation of a brown sticky substance. The resulting mixture was  
then diluted with ethyl acetate (50 mL) and water (50 mL), and the layers were separated.  
The aqueous layer was further extracted with ethyl acetate (2 x 50 mL). The combined



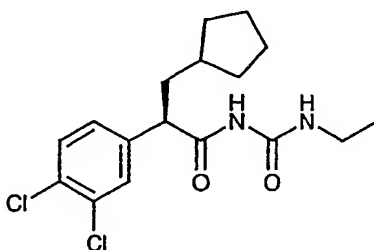
Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/3 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-propionamide (140 mg, 47%) as a yellow foam: mp 72-76°C (foam to gel); FAB-HRMS m/e calcd for  $C_{15}H_{20}N_2O_5S$  (M+H)<sup>+</sup> 341.1172, found 341.1181.

5

A solution of 3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-propionamide (126 mg, 0.37 mmol) and methyl isocyanate (211 mg, 3.70 mmol) in toluene (2 mL) was heated under reflux (120°C) for 15 h. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo*. The resulting yellow oil was treated with a small amount of a 10 1/1 mixture of hexanes/ethyl acetate, and a precipitate started to form. The material was further cooled in the freezer for 2 h to facilitate additional precipitation. The solid was collected by filtration and then dried *in vacuo* to afford 1-[3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-propionyl]-3-methyl-urea (50 mg, 35%) as a pale yellow solid: mp 241-242°C; FAB-HRMS m/e calcd for  $C_{17}H_{23}N_3O_6S$  (M+H)<sup>+</sup> 398.1386, found 15 398.1399.

### Example 141

#### 1-[3-Cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionyl]-3-ethyl-urea



20 A solution of 3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionamide (prepared in Example 139, 103 mg, 0.36 mmol) in toluene (10 mL) was treated with ethyl isocyanate (40  $\mu$ L, 0.54 mmol). The resulting reaction mixture was heated under reflux for 24 h. The reaction mixture was then concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 4/1 hexanes/ethyl acetate) afforded 1-[3-cyclopentyl-2(R)-

and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate) afforded 2-(4-chloro-phenyl)-4-methyl-pentanoic acid ethyl ester (1.24 g, 87.1%) as a white solid: mp 34-35°C; EI-HRMS m/e calcd for C<sub>14</sub>H<sub>19</sub>ClO<sub>2</sub> (M<sup>+</sup>) 254.1074, found 254.1069.

5

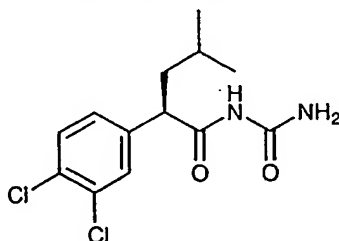
A mixture of 2-(4-chloro-phenyl)-4-methyl-pentanoic acid ethyl ester (508 mg, 1.99 mmol) and urea (239 mg, 3.99 mmol) in a solution of magnesium methoxide in methanol (7.4 wt%, 4.28 mL, 2.99 mmol) was heated to reflux for 24 h. The reaction mixture was then concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate) afforded [2-(4-chloro-phenyl)-4-methyl-pentanoyl]-urea (28.1 mg, 5.2%) as a white solid: mp 164-165°C; EI-HRMS m/e calcd for C<sub>13</sub>H<sub>17</sub>ClN<sub>2</sub>O<sub>2</sub> (M<sup>+</sup>) 268.0979, found 268.0972.

10

## Example 143

15

## R-[2-(3,4-Dichloro-phenyl)-4-methyl-pentanoyl]-urea

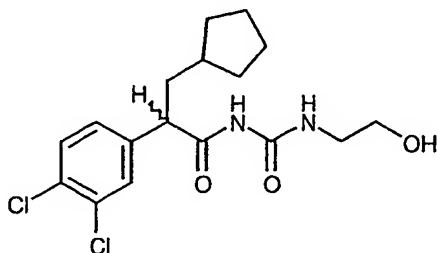


20

A solution of (3,4-dichloro-phenyl)-acetic acid (10.0 g, 0.048 mol) in ethanol (50 mL) was treated with a catalytic amount of sulfuric acid. The reaction mixture was refluxed for 7 h. The reaction was concentrated *in vacuo*, diluted with diethyl ether, and poured into water. The ether layer was washed with a saturated aqueous sodium bicarbonate solution and water. The organics were then dried over sodium sulfate, filtered, and concentrated *in vacuo*. Vacuum distillation (bath temperature: 175°C; head temperature: 125°C) afforded (3,4-dichloro-phenyl)-acetic acid ethyl ester (9.38 g, 82.5%) as a clear oil: EI-HRMS m/e calcd for C<sub>10</sub>H<sub>10</sub>Cl<sub>2</sub>O<sub>2</sub> (M<sup>+</sup>) 232.0058, found 232.0066.

## Example 144

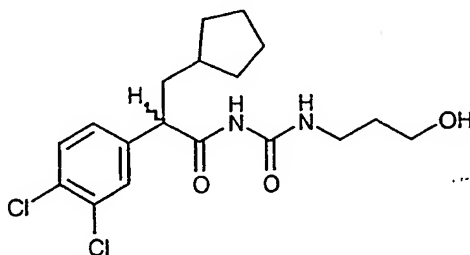
## 1-[3-Cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-(2-hydroxy-ethyl)-urea



- A solution of 1-allyl-3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-urea (prepared in Example 12B-e, 75 mg, 0.20 mmol) in dry methylene chloride (10 mL) and methanol (2 drops, needed to solubilize the compound) was cooled to -78°C and deoxygenated by bubbling argon through the reaction mixture. Ozone was then generated and bubbled through the reaction until a blue color appeared and then the reaction was stirred for five min.
- At this time, argon was bubbled through the solution again until the blue color disappeared. Triphenylphosphine (54 mg, 0.20 mmol) was then added and the reaction warmed to 25°C and stirred for 16 h. At this time, the reaction was concentrated *in vacuo* and then dissolved in dry methanol (10 mL). The reaction was cooled to 0°C and then slowly treated with sodium borohydride (31 mg, 0.81 mmol). The reaction was then warmed to 25°C and stirred for 1 h. It was then quenched with water (10 mL) and extracted with ethyl acetate (3 x 15 mL). The organics were combined and washed with water (1 x 15 mL), a saturated aqueous sodium chloride solution (1 x 15 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate) afforded 1-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-(2-hydroxy-ethyl)-urea (48 mg, 64%) as a hygroscopic white solid: EI-HRMS *m/e* calcd for C<sub>17</sub>H<sub>22</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>3</sub> (M<sup>+</sup>) 370.1215, found 370.1209.

## Example 146

## 1-[3-Cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-(3-hydroxy-propyl)-urea



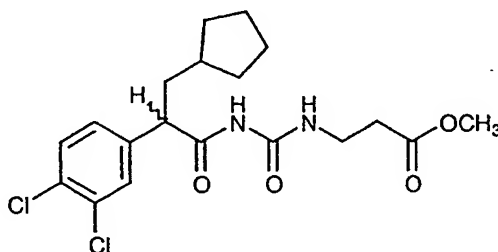
A solution of 1-allyl-3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-urea (prepared  
5 in Example 12B-e, 132 mg, 0.36 mmol) in tetrahydrofuran (10 mL) cooled to 0°C was  
treated with a 1M solution of borane-tetrahydrofuran (0.7 mL, 0.72 mmol). The reaction  
mixture was allowed to slowly warm from 0°C to 25°C over 1 h.. At this time, the  
solution was re-cooled to 0°C and ethanol (2 mL) followed by a mixture of a saturated  
aqueous sodium bicarbonate solution (6 mL) and 30% hydrogen peroxide (2 mL) was  
10 added slowly. This mixture was allowed to slowly warm to 25°C while stirring for 1 h.  
At this time, the reaction was re-cooled to 0°C and slowly quenched with a saturated  
aqueous sodium sulfite solution (20 mL). This solution was extracted with ethyl acetate  
(3 x 20 mL). The organics were washed with a saturated aqueous sodium chloride  
solution (1 x 15 mL), dried over sodium sulfate, and concentrated *in vacuo*. Flash  
15 chromatography (Merck Silica gel 60, 230-400 mesh, 80/20 hexanes/ethyl acetate)  
effected the separation of two spots, the second of the two product spots to elute off the  
column afforded 1-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-(3-hydroxy-  
propyl)-urea (73 mg, 53%) as a white hygroscopic solid: EI-HRMS *m/e* calcd for  
 $C_{18}H_{24}Cl_2N_2O_3$  ( $M^+$ ) 386.1164, found 386.1172.

afforded 3-{3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido}-acetic acid methyl ester (21 mg, 68%) as a white solid: mp 134.5-136.6°C; EI-HRMS m/e calcd for  $C_{18}H_{22}Cl_2N_2O_4$  ( $M^+$ ) 400.0957, found 400.0970.

5

## Example 148

3-{3-[3-Cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido}-propionic acid  
methyl ester



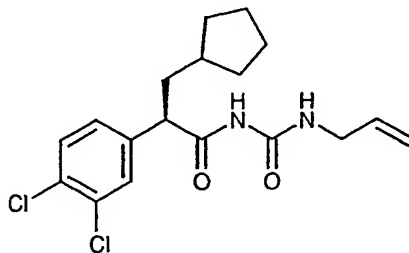
A solution of 3-{3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido}-propionic acid ethyl ester (prepared in Example 12B-c, 94 mg, 0.22 mmol) in ethanol (5 mL) at 25°C was treated with a solution of potassium hydroxide (43 mg, 0.77 mmol) in water (1 mL). This solution was stirred at 25°C for 2 h. At this time, the reaction was diluted with water (5 mL) and the ethanol was removed *in vacuo*. The aqueous layer was acidified to pH = 2 with a 1N aqueous hydrochloric acid solution and extracted with methylene chloride (3 x 15 mL). The organic layers were then dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate plus 1% acetic acid) afforded 3-{3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido}-propionic acid (30 mg, 35%) as a white foam: FAB-HRMS m/e calcd for  $C_{18}H_{22}Cl_2N_2O_4$  ( $M+H$ )<sup>+</sup> 401.1035, found 401.1022.

20

A solution of 3-{3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido}-propionic acid (20 mg, 0.05 mmol) in methanol (5 mL) was treated with concentrated sulfuric acid (4 drops). This solution was heated to 80°C for 8 h. At this time, the reaction was cooled to 25°C and diluted with water (10mL). This solution extracted with ethyl acetate (3 x 20

## Example 150

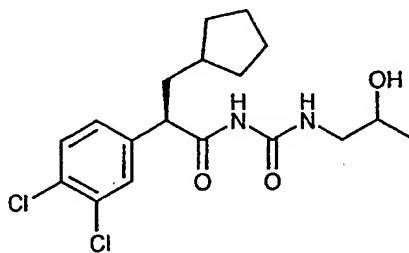
## 1-Allyl-3-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionyl]-urea



A solution of 3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionamide (prepared in  
 5 Example 13, 1.02 g, 3.55 mmol) in toluene (30 mL) was treated with allyl isocyanate  
 (0.47 mL, 5.33 mmol). This solution was heated to reflux for 16 h. At this time, the  
 reaction was cooled to 25°C and concentrated *in vacuo*. Flash chromatography (Merck  
 Silica gel 60, 230-400 mesh, 90/10 hexanes/ethyl acetate) afforded 1-allyl-3-[3-  
 cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionyl]-urea (1.06 g, 81%) as a colorless oil:  
 10  $[\alpha]_{589}^{23} = -25.2^\circ$  ( $c=0.151$ , chloroform); EI-HRMS  $m/e$  calcd for  $C_{18}H_{22}Cl_2N_2O_2$  ( $M^+$ )  
 368.1058, found 368.1054.

## Example 151

## 1-[3-Cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionyl]-3-(2-hydroxy-propyl)-urea



15

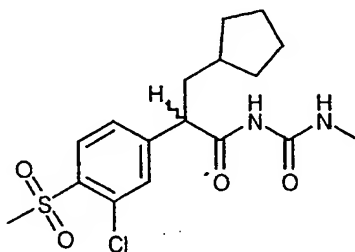
A solution of 1-allyl-3-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionyl]-urea  
 (prepared in Example 24, 765 mg, 2.07 mmol) in tetrahydrofuran (50 mL) cooled to 0°C  
 was treated with a 1.0M borane solution in tetrahydrofuran (4.14 mL, 4.14 mmol). The  
 reaction was allowed to warm from 0°C to 25°C over 1 h. At this time, the reaction was

*vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 80/20 hexanes/ethyl acetate) afforded 1-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-(3-hydroxy-propyl)-urea (173 mg, 22%) as a white foam:  $[\alpha]_{589}^{23} = -37.3^\circ$  ( $c=0.075$ , chloroform); EI-HRMS  $m/e$  calcd for  $C_{18}H_{24}Cl_2N_2O_3$  ( $M^+$ ) 386.1164, found 386.1154.

5

### Example 153

#### 1-[2-(3-Chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea



A solution of aluminum trichloride (34.8 g, 261.4 mmol) in chloroform (120 mL) cooled  
10 to 0°C was treated with a solution of ethyl chlorooxoacetate (18.7 mL, 167.5 mmol) in  
chloroform (120 mL). The mixture was stirred at 0°C for 30 min. At this time, a solution  
of 2-chlorothioanisole (25.0 g, 156.5 mmol) in chloroform (120 mL) was added dropwise  
to the reaction mixture. It was then allowed to warm to 25°C and stirred for an additional  
3.5 h at 25°C. At this time, the reaction was quenched by the slow addition of water (500  
15 mL) and extracted with chloroform (3 x 50 mL). The organics were dried over sodium  
sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60,  
230-400 mesh, 80/20 hexanes/ethyl acetate) afforded (3-chloro-4-methylsulfonyl-phenyl)-  
oxo-acetic acid ethyl ester (31.37 g, 77%) as a yellow oil: EI-HRMS  $m/e$  calcd for  
 $C_{18}H_{24}Cl_2N_2O_3$  ( $M^+$ ) 386.1164, found 386.1154.

20

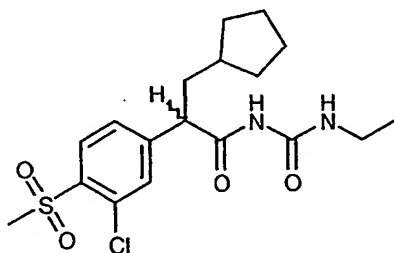
A solution of cyclopentylmethyl triphenylphosphonium iodide (prepared in Example 33,  
725 mg, 1.53 mmol) in tetrahydrofuran (10 mL) cooled to 0°C was treated with a 1.0M  
solution of sodium bis(trimethylsilyl)amide in tetrahydrofuran (2.14 mL, 2.14 mmol).

concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 75/25 hexanes/ethyl acetate) afforded a mixture of 2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid methyl ester and 2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid ethyl ester (transesterification occurred under the reaction conditions) (937 mg) as a clear colorless oil. (Transesterification occurred under the reaction conditions and the mixture of esters was carried on without characterization)

A solution of 2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid methyl ester and 2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid ethyl ester (268 mg) and methyl urea (110 mg, 1.5 mmol) in magnesium methoxide in methanol (7.4 wt%, 1.6 mL, 1.1 mmol) was heated to 100°C for 8 h. At this time, the reaction was concentrated *in vacuo*. The residue was then dissolved in ethyl acetate (50 mL), filtered through a plug of silica gel, and washed with ethyl acetate (100 mL). The filtrate was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 60/40 hexanes/ethyl acetate) afforded 1-[2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea (55 mg, 19% yield) as a white foam: FAB-HRMS  $m/e$  calcd for  $C_{17}H_{23}ClN_2O_4S$  (M+H)<sup>+</sup> 387.1145, found 387.1156.

#### Example 154

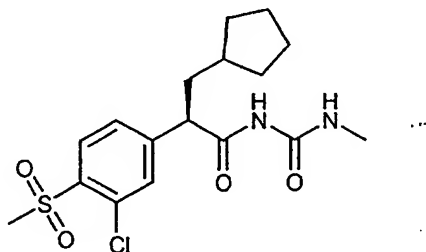
20 1-[2-(3-Chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionyl]-3-ethyl-urea



A solution of 2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid methyl ester and 2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid ethyl ester (prepared in Example 27, 937 mg) in ethanol (30 mL) at 25°C was treated with



## Example 155

1-[2(R)-(3-Chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionyl]-3-methyl  
urea

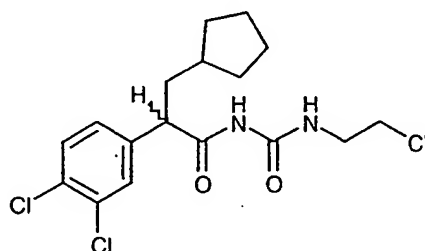
- 5 A solution of 2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid (prepared in Example 28, 6.1 g, 18.3 mmol), (R)-(+)-4-benzyl-2-oxazolidinone (2.83g, 15.9 mmol), triethylamine (6.68 mL, 47.7 mmol), in toluene (50 mL) heated to 80°C was treated with pivaloyl chloride (3.55 mL, 28.8 mmol) in toluene (10 mL). The resulting slurry was heated at 80°C for 36 h. At this time, the reaction was cooled to 20°C and
- 10 concentrated *in vacuo*. The residue was diluted with ethyl acetate (150 mL) washed with a 1N aqueous hydrochloric acid solution (100 mL), a 10% aqueous sodium carbonate solution (100 mL), and a saturated aqueous sodium chloride solution (100 mL). The organics were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 90/5/5 methylene
- 15 chloride/hexanes/ethyl acetate) afforded 4(R)-benzyl-3-[2(S)-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionyl]-oxazolidin-2-one (2.08 g, 23%) as a white foam:  $[\alpha]_{589}^{23} = +10.4^\circ$  (c=0.144, chloroform); FAB-HRMS m/e calcd for  $C_{25}H_{28}ClNO_5S$  (M+H)<sup>+</sup> 490.1455, found 490.1457 and 4(R)-benzyl-3-[2(R)-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionyl]-oxazolidin-2-one (2.20 g, 25%) as a
- 20 white foam:  $[\alpha]_{589}^{23} = -93.9^\circ$  (c=0.165, chloroform); FAB-HRMS m/e calcd for  $C_{25}H_{28}ClNO_5S$  (M+H)<sup>+</sup> 490.1455, found 490.1443.

A solution of lithium hydroxide (215 mg, 9.0 mmol) in water (2.8 mL) was treated with a 30% aqueous solution of hydrogen peroxide (2.0 mL, 18 mmol). This lithium

1.94 mmol). The reaction mixture was then heated at 100°C for 16 h. At this time, the reaction was concentrated *in vacuo*. Biotage chromatography (FLASH 40S, Silica, 60/40 hexanes/ethyl acetate) afforded 1-[2(R)-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea (79 mg, 42%) as a white foam:  $[\alpha]_{D}^{25} = -8.9^\circ$  (c=0.09, chloroform); FAB-HRMS m/e calcd for  $C_{17}H_{23}ClN_2O_4S$  (M+H)<sup>+</sup> 387.1145, found 387.1142.

### Example 156

#### 1-(2-Chloro-ethyl)-3-[3-cyclopentyl-2-(3,4-dichlorophenyl)-propionyl]-urea



10

A solution of 3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionamide (prepared in Example 12, 182 mg, 0.64 mmol) in toluene (10 mL) was treated with 2-chloroethyl isocyanate (0.08 mL, 0.95 mmol). The reaction was heated at reflux for 16 h. At this time, the reaction was cooled to 25°C and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 90/10 hexanes/ethyl acetate) afforded 1-(2-chloro-ethyl)-3-[3-cyclopentyl-2-(3,4-dichlorophenyl)-propionyl]-urea (189 mg, 76%) as a colorless oil: EI-HRMS m/e calcd for  $C_{17}H_{21}Cl_3N_2O_2$  (M<sup>+</sup>) 390.0669, found 390.0659.

15

concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 8/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(3-trifluoromethylsulfanyl-phenyl)-propionic acid methyl ester (2.95 g, 89%) as a colorless oil: EI-HRMS *m/e* calcd for  $C_{16}H_{19}F_3O_2S$  ( $M^+$ ) 332.1058, found 332.1047.

5

A solution of 3-cyclopentyl-2-(3-trifluoromethylsulfanyl-phenyl)-propionic acid methyl ester (2.75 g, 8.27 mmol) in methylene chloride (30 mL) was treated with 3-chloroperoxybenzoic acid (80-85% grade, 4.28 g based on 80%, 20.67 mmol). The reaction mixture was stirred at 25°C for 6 h. At this time, thin layer chromatography showed the presence of two new lower  $R_f$  products. An additional 4.00 g of 3-chloroperoxybenzoic acid was added to the reaction mixture to drive the conversion of the sulfoxide to the sulfone, and the resulting reaction mixture was stirred at 40°C for 3 d. The reaction mixture was cooled to 25°C and then partitioned between water (100 mL) and methylene chloride (100 mL). The layers were shaken and separated. The organic phase was washed twice with a saturated aqueous sodium bicarbonate solution, washed with water, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/methylene chloride) afforded 3-cyclopentyl-2-(3-trifluoromethanesulfonyl-phenyl)-propionic acid methyl ester (2.07 g, 69%) as a colorless oil: EI-HRMS *m/e* calcd for  $C_{16}H_{19}F_3O_4S$  ( $M^+$ ) 364.0956, found 364.0947.

3-Cyclopentyl-2-(3-trifluoromethanesulfonyl-phenyl)-propionic acid methyl ester (500 mg, 1.37 mmol) and methyl urea (305 mg, 4.12 mmol) were treated with a solution of magnesium methoxide in methanol (7.4 wt%, 5.9 mL, 4.12 mmol). The reaction mixture was then concentrated *in vacuo* to approximately one-half the volume of methanol. The resulting reaction mixture was then heated under reflux for 15 h. The reaction mixture was allowed to cool to 25°C, diluted with ethyl acetate (10 mL), and then filtered through celite. The celite was thoroughly washed with ethyl acetate. The filtrate was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 3/1

25

quenched with a saturated aqueous ammonium chloride solution (10 mL) and then partitioned between water (75 mL) and ethyl acetate (75 mL). The layers were shaken and separated. The aqueous layer was further extracted with ethyl acetate (75 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 5/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(3-fluoro-4-trifluoromethyl-phenyl)-propionic acid methyl ester (2.69 g, 83%) as a colorless oil: EI-HRMS *m/e* calcd for  $C_{16}H_{18}F_4O_2$  ( $M^+$ ) 318.1243, found 318.1250.

10 3-Cyclopentyl-2-(3-fluoro-4-trifluoromethyl-phenyl)-propionic acid methyl ester (750 mg, 2.36 mmol) and methyl urea (437 mg, 5.90 mmol) were treated with a solution of magnesium methoxide in methanol (7.4 wt%, 14.5 mL, 7.08 mmol). The reaction mixture was then concentrated *in vacuo* to approximately one-half the volume of methanol. The resulting reaction mixture was then heated under reflux for 15 h. The reaction mixture was allowed to cool to 25°C and then partitioned between water (75 mL) and ethyl acetate (75 mL). An emulsion formed, and a saturated aqueous sodium chloride solution was added to break down the emulsion. The aqueous layer was further extracted with ethyl acetate (2 x 75 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford a white semi-solid. The semi-solid was treated with a solution of 2/1 hexanes/ethyl acetate, and a white solid formed. The solid was filtered, washed well with hexanes, and dried to afford 1-[3-cyclopentyl-2-(3-fluoro-4-trifluoromethyl-phenyl)-propionyl]-3-methyl-urea (322 mg, 38%) as a white solid: mp 187-189°C; FAB-HRMS *m/e* calcd for  $C_{17}H_{20}F_4N_2O_2$  ( $M+H$ )<sup>+</sup> 361.1539, found 361.1549.

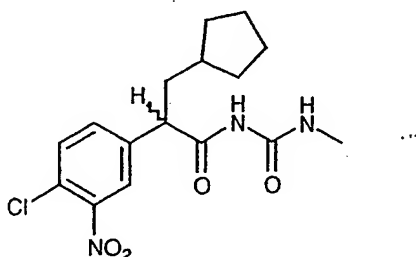
86%) as a light orange solid: mp 195-198°C; FAB-HRMS m/e calcd for  $C_{24}H_{26}P$  (M+H)<sup>+</sup> 345.1772, found 345.1784.

A suspension of cyclopentylmethyl triphenylphosphonium iodide (24.48 g, 51.82 mmol) in tetrahydrofuran (100 mL) cooled to 0°C was treated dropwise with a 1.0M solution of sodium bis(trimethylsilyl)amide in tetrahydrofuran (52 mL, 51.82 mmol). The bright orange reaction mixture was stirred at 0°C for 1 h. The reaction mixture was then treated with (4-ethylsulfanyl-phenyl)-oxo-acetic acid ethyl ester (9.50 g, 39.87 mmol). The resulting reaction mixture was allowed to warm to 25°C where it was stirred for 20 h. The reaction mixture was concentrated *in vacuo* to remove tetrahydrofuran and then diluted with water (300 mL). The aqueous layer was extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (1 x 200 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 19/1 hexanes/ethyl acetate) afforded the 3-cyclopentyl-2-(4-ethylsulfanyl-phenyl)-acrylic acid ethyl ester (6.08 g, 50%) as a yellow oil containing a 1.82:1 mixture of E:Z isomers: FAB-LRMS m/e calcd for  $C_{18}H_{24}O_2S$  (M+H)<sup>+</sup> integer mass 304, found 305.

A solution of 3-cyclopentyl-2-(4-ethylsulfanyl-phenyl)-acrylic acid ethyl ester [5.76 g, 18.92 mmol, E:Z = 1.82:1] in methylene chloride (47 mL) was slowly treated with 3-chloroperoxybenzoic acid (57-86% grade, 11.45 g based on 57%, 37.83 mmol). The reaction mixture was stirred at 25°C for 1 h. The reaction mixture was concentrated *in vacuo* to remove methylene chloride. The resulting residue was diluted with diethyl ether (300 mL). The organic phase was washed with a saturated aqueous sodium bicarbonate solution (3 x 200 mL), washed with a saturated aqueous sodium chloride solution (1 x 200 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 3/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-ethanesulfonyl-phenyl)-acrylic acid ethyl ester (4.89 g, 77%) as a

## Example 160

## 1-[2-(4-Chloro-3-nitro-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea



- 5 A solution of 4-chloro-3-nitrophenylacetamide (2.00 g, 9.32 mmol) in methanol (40 mL) was treated with Amberlyst® 15 ion exchange resin (15.00 g). The resulting reaction mixture was heated under reflux for 64 h. The reaction mixture was allowed to cool to 25°C and then filtered to remove the Amberlyst® 15 ion exchange resin. The filtrate was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 3/1  
10 hexanes/ethyl acetate) afforded 4-chloro-3-nitro-phenylacetic acid methyl ester (1.91 g, 89%) as a yellow oil: EI-HRMS *m/e* calcd for C<sub>9</sub>H<sub>8</sub>ClNO<sub>4</sub> (M<sup>+</sup>) 229.0142, found 229.0146.

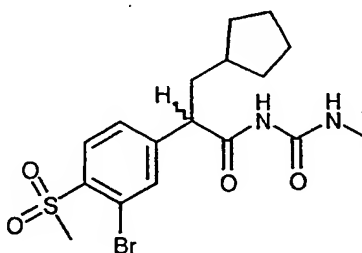
- A solution of diisopropylamine (3.35 mL, 23.9 mmol) in dry tetrahydrofuran (45 mL) and  
15 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (15 mL) cooled to -78°C was treated dropwise with a 2.5M solution of *n*-butyllithium in hexanes (9.56 mL, 23.9 mmol) over a 10 min period. The pale yellow reaction mixture was stirred at -78°C for 20 min. At this time, the reaction was treated with a solution of 4-chloro-3-nitrophenylacetic acid methyl ester (5.00 g, 21.8 mmol) in a small amount of tetrahydrofuran over a 15 min period. The  
20 reaction mixture turned deep purple (almost black) in color. The reaction mixture was then stirred at -78°C for 1 h. At this time, the reaction was treated with a solution of iodomethylcyclopentane (4.58 g, 21.8 mol) in a small amount of dry tetrahydrofuran. The reaction mixture was then stirred at -78°C and then allowed to warm to 25°C, where it was stirred for 48 h. The reaction mixture was then quenched with a saturated aqueous

acid solution and a saturated aqueous sodium chloride solution. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford 2-(4-chloro-3-nitro-phenyl)-3-cyclopentyl-propionamide (295 mg, 67%) as a yellow oil which solidified upon sitting to a yellow solid. The yellow solid was used without further purification: mp 112-114°C; EI-HRMS *m/e* calcd for  $C_{14}H_{17}ClN_2O_3$  ( $M^+$ ) 296.0927, found 296.0931.

A solution of 2-(4-chloro-3-nitro-phenyl)-3-cyclopentyl-propionamide (200 mg, 0.67 mmol) and methyl isocyanate (382 mg, 6.70 mmol) in toluene (3 mL) was heated under reflux (120°C) for 15 h. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 2/1 hexanes/ethyl acetate) afforded 1-[2-(4-chloro-3-nitro-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea (139 g, 60%) as a white foam: mp 61-64°C (foam to gel); FAB-HRMS *m/e* calcd for  $C_{16}H_{20}ClN_3O_4$  ( $M+H$ )<sup>+</sup> 354.1220, found 354.1232.

### Example 161

#### 1-[2-(3-Bromo-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea



A solution of 4-(methylthio)phenylacetic acid (21.21 g, 116.38 mmol) in methanol (291 mL) was treated slowly with concentrated sulfuric acid (3 mL). The resulting reaction mixture was heated under reflux for 3 d. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo* to remove methanol. The resulting residue was diluted with diethyl ether (600 mL). The organic layer was washed with a saturated aqueous sodium bicarbonate solution (3 x 300 mL) and a saturated aqueous sodium chloride solution (1 x 300 mL). The organic layer was dried over sodium sulfate, filtered,

remaining aqueous phase was extracted with ethyl acetate (3 x 150 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (1 x 200 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 19/1 hexanes/ethyl acetate) afforded  
5 2-(3-bromo-4-methylsulfanyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (4.52 g, 57%) as a light yellow oil: EI-HRMS *m/e* calcd for  $C_{16}H_{21}BrO_2S$  ( $M^+$ ) 356.0446, found 356.0435.

A solution of 2-(3-bromo-4-methylsulfanyl-phenyl)-3-cyclopentyl-propionic acid methyl  
10 ester (1.07 g, 2.99 mmol) in methylene chloride (15 mL) was treated with 3-chloroperoxybenzoic acid (57-86% grade, 1.81 g based on 57%, 5.99 mmol). The reaction mixture was stirred at 25°C for 3 h. The reaction mixture was concentrated *in vacuo* to remove methylene chloride. The resulting residue was diluted with diethyl ether (300 mL). The organic phase was washed with a saturated aqueous sodium bicarbonate  
15 solution (3 x 200 mL) and a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/1 hexanes/ethyl acetate) afforded 2-(3-bromo-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (1.09 g, 94%) as a colorless oil: EI-HRMS *m/e* calcd for  $C_{16}H_{19}BrO_4S$  ( $M^+$ ) 388.0344, found 388.0343.

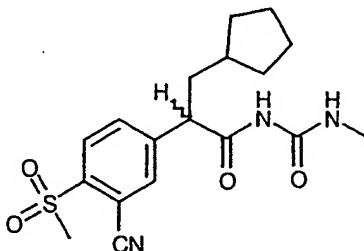
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A solution of 2-(3-bromo-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (1.62 g, 4.16 mol) in methanol (10 mL) was treated with a 1N aqueous sodium hydroxide solution (8.7 mL, 8.74 mol). The reaction mixture was stirred at 25°C for 27 h. The reaction mixture was concentrated *in vacuo* to remove methanol. The  
25 resulting aqueous residue was acidified to pH = 2 with a 10% aqueous hydrochloric acid solution and then extracted with ethyl acetate (1 x 400 mL). The organic layer was washed with water (1 x 300 mL) and washed with a saturated aqueous sodium chloride solution (1 x 300 mL). The organic layer was then dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford 2-(3-bromo-4-methanesulfonyl-phenyl)-3-cyclopentyl-



## Example 162

## 1-[2-(3-Cyano-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea



A solution of 4-(methylthio)phenylacetic acid (21.21 g, 116.38 mmol) in methanol (291 mL) was treated slowly with concentrated sulfuric acid (3 mL). The resulting reaction mixture was heated under reflux for 3 d. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo* to remove methanol. The resulting residue was diluted with diethyl ether (600 mL). The organic layer was washed with a saturated aqueous sodium bicarbonate solution (3 x 300 mL) and a saturated aqueous sodium chloride solution (1 x 300 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford (4-methylsulfanyl-phenyl)-acetic acid methyl ester (20.95 g, 92%) as a yellow liquid which was used without further purification: EI-HRMS m/e calcd for C<sub>10</sub>H<sub>12</sub>O<sub>2</sub>S (M<sup>+</sup>) 196.0558, found 196.0559.

A solution of (4-methylsulfanyl-phenyl)-acetic acid methyl ester (5.11 g, 26.03 mmol) in carbon tetrachloride (130 mL) was treated slowly with bromine (1.74 mL, 33.84 mmol). The reaction mixture was stirred at 25°C for 4 h, at which time, thin layer chromatography still indicated the presence of a substantial amount of starting material. The reaction mixture was further treated with more bromine (1.74 mL, 33.84 mmol). The reaction mixture was stirred an additional 4 h at 25°C and then quenched with a 10% aqueous sodium bisulfite solution (150 mL). The reaction mixture was concentrated *in vacuo* to remove carbon tetrachloride. The resulting aqueous layer was extracted with ethyl acetate (3 x 150 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230

dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/1 hexanes/ethyl acetate) afforded 2-(3-bromo-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (1.09 g, 94%) as a colorless oil: EI-HRMS *m/e* calcd for  $C_{16}H_{19}BrO_4S$  ( $M^+$ ) 388.0344, found 388.0343.

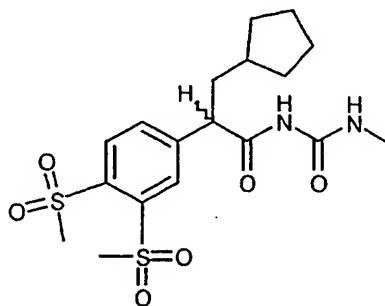
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A mixture of 2-(3-bromo-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (990.0 mg, 2.54 mmol) and copper(I) cyanide (273.3 mg, 3.05 mmol) in dry *N,N*-dimethylformamide (2.5 mL) was heated under reflux for 4 h. The reaction was allowed to cool to 25°C, and the crude reaction mixture was directly purified without further  
10 chemical work-up. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 100% hexanes then 3/1 hexanes/ethyl acetate) afforded 2-(3-cyano-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (646.5 mg, 76%) as a pale yellow oil: EI-HRMS *m/e* calcd for  $C_{17}H_{21}NO_4S$  ( $M^+$ ) 335.1191, found 335.1185.

15 A solution of 2-(3-cyano-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (4.84 g, 14.4 mol) in tetrahydrofuran (25 mL) was treated with a 0.8M aqueous lithium hydroxide solution (27 mL, 21.6 mmol). The reaction mixture was stirred at 25°C for 2.5 h. The reaction mixture was partitioned between water and ethyl acetate and then acidified to pH = 2 with a 10% aqueous hydrochloric acid solution. The layers were  
20 shaken and separated. The resulting organic layer was washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford crude 2-(3-cyano-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid (3.80 g, 82%) as a pale yellow oil that solidified to a pale yellow solid. An analytical sample was obtained by recrystallization from ethyl acetate to afford 2-(3-cyano-4-  
25 methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid as a white solid: mp 180-181°C; EI-HRMS *m/e* calcd for  $C_{16}H_{19}NO_4S$  ( $M^+$ ) 321.1034, found 321.1039.

## Example 163

## 1-[2-(3,4-Bis-methanesulfonyl-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea



A solution of 3,4-difluorophenylacetic acid (5.00 g, 29.05 mmol) in methanol (73 mL)  
5 was slowly treated with concentrated sulfuric acid (4 mL). The resulting reaction mixture  
was heated under reflux for 65 h. The reaction mixture was allowed to cool to 25°C and  
then concentrated *in vacuo* to remove methanol. The resulting residue was slowly diluted  
with a saturated aqueous sodium bicarbonate solution (300 mL) and then extracted with  
ethyl acetate (1 x 300 mL). The organic layer was dried over magnesium sulfate, filtered,  
10 and concentrated *in vacuo* to afford (3,4-difluoro-phenyl)-acetic acid methyl ester (5.38 g,  
99%) as a yellow oil which was used without further purification.

A solution of sodium thiomethoxide (6.39 g, 86.69 mmol) in dimethyl sulfoxide (72 mL)  
was treated with (3,4-difluoro-phenyl)-acetic acid methyl ester (5.38 g, 28.89 mmol). The  
15 reaction mixture was stirred at 25°C for 2 h and then at 70°C for 15 min. At this time,  
thin layer chromatography indicated the absence of starting material and the presence of a  
very polar new product. The reaction indicated that the ester hydrolyzed to the acid upon  
heating. The resulting reaction mixture was allowed to cool to 25°C. The reaction  
mixture was then treated with a 10% aqueous hydrochloric acid solution (200 mL) and  
20 then extracted with chloroform (3 x 200 mL). The combined organic layers were dried  
over magnesium sulfate, filtered, and concentrated *in vacuo* to afford a yellow oil. This  
yellow oil was dissolved in methanol (100 mL) and then slowly treated with concentrated  
sulfuric acid (5 mL). The resulting reaction mixture was heated under reflux for 3 h. The

hexanes/ethyl acetate) afforded an inseparable, isomeric mixture of (3-methanesulfonyl-4-methylsulfonyl-phenyl)-acetic acid methyl ester and (4-methanesulfonyl-3-methylsulfonyl-phenyl)-acetic acid methyl ester as a yellow liquid (2.19 g, 86%) which was used without further purification and characterization.

5

A solution of the inseparable, isomeric mixture of (3-methanesulfonyl-4-methylsulfonyl-phenyl)-acetic acid methyl ester and (4-methanesulfonyl-3-methylsulfonyl-phenyl)-acetic acid methyl ester (2.19 g, 7.98 mmol) in methylene chloride (20 mL) was slowly treated with 3-chloroperoxybenzoic acid (57-86% grade, 6.41 g based on 57%, 31.93 mmol).

- 10 The reaction mixture was stirred at 25°C for 5 h and then slowly quenched with a 1.5N aqueous sodium sulfite solution. The resulting reaction mixture was extracted with methylene chloride (300 mL). The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 10/1 methylene chloride/ethyl acetate) afforded (3,4-bis-methanesulfonyl-phenyl)-  
15 acetic acid methyl ester (1.89 g, 77%) as a white solid: mp 157-158°C; EI-HRMS *m/e* calcd for C<sub>11</sub>H<sub>14</sub>O<sub>6</sub>S<sub>2</sub> (M<sup>+</sup>) 306.0232, found 306.0234.

- A solution of diisopropylamine (951 µL, 6.79 mmol) in dry tetrahydrofuran (6 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (2 mL) was cooled to -78°C under  
20 nitrogen and then treated with a 2.5M solution of *n*-butyllithium in hexanes (2.5 mL, 6.79 mmol). The resulting reaction mixture was stirred at -78°C for 30 min and then treated dropwise with a solution of (3,4-bis-methanesulfonyl-phenyl)-acetic acid methyl ester (1.89 g, 6.17 mmol) in dry tetrahydrofuran (12 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (4 mL). The resulting reaction mixture was allowed to stir at -78°C  
25 for 1 h. At this time, the reaction was treated with a solution of iodomethylcyclopentane (1.56 g, 7.40 mmol) in a small amount of dry tetrahydrofuran. The reaction mixture was allowed to warm to 25°C where it was stirred for 64 h. The reaction mixture was quenched with water (150 mL) and then concentrated *in vacuo* to remove tetrahydrofuran. The remaining residue was further diluted with water (100 mL) and then extracted with

A solution of freshly prepared lithium diisopropylamide (35.3 mL of a 0.31M stock solution, 10.9 mmol) cooled to -78°C was treated with (4-fluoro-3-trifluoromethyl-phenyl)-acetic acid (1.11 g, 5.0 mmol) in tetrahydrofuran/1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (12.4 mL, 3:1). The resulting solution was stirred at -78°C for 1 h.

5 At this time, the reaction was treated with a solution of iodomethylcyclopentane (1.16 g, 5.52 mmol) in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (1.2 mL). The reaction mixture was stirred at -78°C for 4 h. The reaction was then warmed to 25°C and was stirred at 25°C for 48 h. This solution was then quenched by the slow addition of the reaction mixture to an aqueous solution of 2N hydrochloric acid (50 mL). The product

10 was extracted into ethyl acetate (3 x 100 mL) and diethyl ether (1 x 50 mL). The organic layers were dried over magnesium sulfate and sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate with acetic acid) afforded 3-cyclopentyl-2-(4-fluoro-3-trifluoromethyl-phenyl)-propionic acid (1.28 g, 84.3%) as a white solid: mp 66-68°C: EI-

15 HRMS *m/e* calcd for C<sub>15</sub>H<sub>16</sub>F<sub>4</sub>O<sub>2</sub> (M<sup>+</sup>) 305.1165, found 305.1174.

A solution 3-cyclopentyl-2-(4-fluoro-3-trifluoromethyl-phenyl)-propionic acid (304 mg, 1.0 mmol) in methylene chloride (10 mL) and *N,N*-dimethylformamide (1 drop) was cooled to 0°C and then treated with a 2.0M solution of oxalyl chloride in methylene

20 chloride (1.5 mL, 3.0 mmol). The reaction was stirred for 30 min at 0°C. At this time, 1,1,1,3,3,3-hexamethyldisilazane (2.0 mL, 9.5 mmol) was added to the reaction mixture. The reaction was allowed to slowly warm to 25°C and then stirred at 25°C for 16 h. The reaction mixture was then treated with methanol (3 mL) and diluted with methylene chloride (35 mL). The resulting mixture was washed with a 5% aqueous sulfuric acid

25 solution (2 x 10 mL), water (1 x 25 mL), and a saturated aqueous sodium chloride solution (3 x 25 mL). The organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford 3-cyclopentyl-2-(4-fluoro-3-trifluoromethyl-phenyl)-propionamide (333 mg, 92.5%) as a pale yellow oil: EI-HRMS *m/e* calcd for C<sub>15</sub>H<sub>17</sub>F<sub>4</sub>NO (M<sup>+</sup>) 303.1246, found 303.1252.

acid ethyl ester (28.30 g, 77.2%) as an yellow oil: EI-HRMS m/e calcd for  $C_{16}H_{21}NO_4$  ( $M^+$ ) 291.1470, found 291.1470.

A solution of 3-cyclopentyl-2-(4-nitro-phenyl)-propionic acid ethyl ester (7.37 g, 25.3 mmol) in ethyl acetate (316 mL) was treated with 10% palladium on activated carbon (500 mg). The reaction mixture was stirred under hydrogen gas at 60 psi at 25°C for 18 h. The catalyst was then filtered off through a pad of celite (ethyl acetate). The filtrate was concentrated *in vacuo* to give 2-(4-amino-phenyl)-3-cyclopentyl-propionic acid ethyl ester (3.52 g, 53.3%) as a yellow oil: EI-HRMS m/e calcd for  $C_{16}H_{23}NO_2$  ( $M^+$ ) 261.1727, found 261.1727.

A mixture of concentrated hydrochloric acid (0.38 mL) and ice (380 mg) cooled to 0°C was treated with 2-(4-amino-phenyl)-3-cyclopentyl-propionic acid ethyl ester (497 mg, 1.90 mmol). After 5 min, a solution of sodium nitrite (139 mg, 2.0 mmol) in water (0.31 mL) was added to the reaction mixture. The resulting solution was stirred at 0°C for 5 min. At this time, this solution was added to a solution of *n*-butyl mercaptan (0.23 mL, 2.20 mmol) in water (0.4 mL) warmed to 45°C. The reaction was stirred at 45°C for 3 h. At this time, the reaction was diluted with water (50 mL) and extracted with methylene chloride (3 x 50 mL). The organics were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude brown oil (588 mg) in methylene chloride (16.5 mL) was cooled to 0°C and treated with 3-chloroperoxybenzoic acid (80-85% grade, 1.5 g, 8.78 mmol). The reaction mixture was stirred at 25°C for 48 h. At this time, the reaction was diluted with methylene chloride (100 mL). This solution was washed with a saturated aqueous sodium bisulfite solution (1 x 100 mL), a saturated aqueous sodium chloride solution (1 x 100 mL), a saturated aqueous sodium bicarbonate solution (1 x 100 mL), and a saturated aqueous sodium chloride solution (1 x 100 mL). The organics were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 80/20 hexanes/ethyl acetate) afforded 2-[4-(butane-

was stirred at 25°C for 48 h. This solution was then quenched by the slow addition of the reaction mixture to an aqueous solution of 2N hydrochloric acid (50 mL). The product was extracted into ethyl acetate (3 x 100 mL) and diethyl ether (1 x 50 mL). The organics were dried over magnesium sulfate and sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate with acetic acid) afforded 3-cyclopentyl-2-(4-fluoro-3-trifluoromethyl-phenyl)-propionic acid (1.28 g, 84.3%) as a white solid: mp 66-68°C; EI-HRMS *m/e* calcd for  $C_{15}H_{16}F_4O_2 (M^+)$  305.1165, found 305.1174.

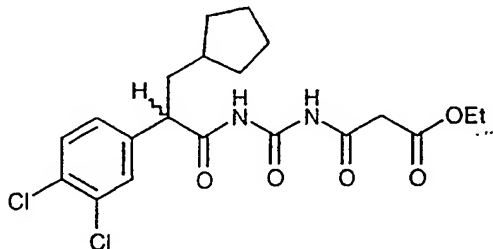
10 A solution of 3-cyclopentyl-2-(4-fluoro-3-trifluoromethyl-phenyl)-propionic acid (7.77 g, 25.3 mmol) in methanol (50 mL) was treated slowly with concentrated sulfuric acid (0.01 mL). The resulting reaction mixture was heated under reflux for 24 h. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo*. The residue was dissolved in ethyl acetate (75 mL) and washed with a saturated aqueous sodium bicarbonate solution (1 x 50 mL), water (1 x 50 mL), and a saturated aqueous sodium chloride solution (4 x 50 mL). The organics were dried over magnesium sulfate and sodium sulfate, filtered, and concentrated *in vacuo* to afford 3-cyclopentyl-2-(4-fluoro-3-trifluoromethyl-phenyl)-propionic acid methyl ester (8.48 g, 87.5%) as yellow oil: EI-HRMS *m/e* calcd for  $C_{16}H_{18}F_4O_2 (M^+)$  318.1243, found 318.1240.

20

A solution of 3-cyclopentyl-2-(4-fluoro-3-trifluoromethyl-phenyl)-propionic acid methyl ester (7.0 g, 21.9 mmol) in *N,N*-dimethylformamide (50 mL) was treated with sodium methanethiolate (2.61 g, 33.0 mmol). The reaction mixture was then heated to 100-110°C for 24 h. At this time, the reaction was poured onto a mixture of ice and an aqueous solution of 2N hydrochloric acid (100 mL). This mixture was extracted into ethyl acetate (3 x 75 mL) and diethyl ether (1 x 50 mL). The organics were then washed with water (1 x 75 mL) and a saturated aqueous sodium chloride solution (3 x 100 mL). The organics were dried over magnesium sulfate and sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 85/15

## Example 167

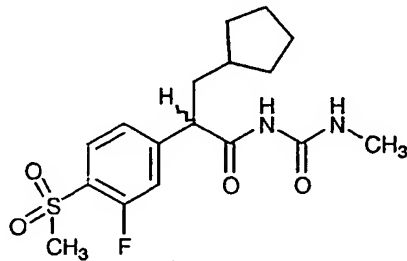
**3-{3-[3-Cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido}-3-oxo-propionic acid  
ethyl ester**



- 5 A solution of [3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-urea (prepared in Example 1B-d, 402 mg, 1.22 mmol) and pyridine (0.15 mL, 1.83 mmol) in toluene (15 mL) was treated with ethyl malonyl chloride (0.19 mL, 1.5 mmol). The resulting reaction mixture was heated at reflux for 2 h. At this time, additional pyridine (0.15 mL, 1.83 mmol) and ethyl malonyl chloride (0.19 mL, 1.5 mmol) were added. The reaction was
- 10 then heated at reflux for 90 min. The reaction was then cooled to 25°C, diluted with ethyl acetate (50 mL), washed with water (2 x 25 mL), and dried over magnesium sulfate. The solution was concentrated *in vacuo*. Flash column chromatography (Merck Silica gel 60, 230-400 mesh, 4/1 hexane/ethyl acetate) afforded 3-{3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido}-3-oxo-propionic acid ethyl ester (172 mg, 32%) as a colorless
- 15 gum: EI-HRMS *m/e* calcd for C<sub>20</sub>H<sub>24</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>5</sub> (M<sup>+</sup>) 443.1140, found 443.1128.

## Example 168

**1-[3-Cyclopentyl-2-(3-fluoro-4-methanesulfonyl-phenyl)-propionyl]-3-methyl-urea**





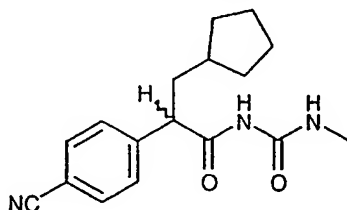
A solution of 2-(4-chloro-3-nitrophenyl)-3-cyclopentyl-propionic acid methyl ester (1.00 g, 3.21 mmol) and sodium methanesulfinate (0.36 g, 3.53 mmol) in dimethyl sulfoxide (3 mL) was heated at 130°C for 5 h. The black reaction mixture was then poured over ice (20 g), resulting in the formation of a brown sticky substance. The resulting mixture was then treated with ethyl acetate (50 mL) and water (50 mL), and the layers were separated. The aqueous layer was further extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-propionic acid methyl ester (0.95 g, 84%) as a yellow gel: FAB-HRMS *m/e* calcd for  $C_{16}H_{21}NO_6S$  ( $M+H$ )<sup>+</sup> 356.1169, found 356.1175.

A solution of 3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-propionic acid methyl ester (1.50 g, 4.22 mmol) in methanol (30 mL) was treated with a solution of ammonium chloride (474 mg, 8.86 mmol) in water (3 mL). The reaction mixture was stirred at 25°C for 5 min and then treated with zinc dust (2.70 g, 41.36 mmol). The reaction mixture was heated under reflux for 2 h. The reaction mixture was allowed to cool to 25°C and then filtered through a pad of celite. The filtrate was concentrated *in vacuo*. The resulting orange oil was dissolved in ethyl acetate, dried over magnesium sulfate, filtrated, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 2/1 hexanes/ethyl acetate) afforded 2-(3-amino-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (1.49 g, 98%) as a white solid: mp 98-100°C; EI-HRMS *m/e* calcd for  $C_{16}H_{23}NO_4S$  ( $M^+$ ) 325.1348, found 325.1358.

A slurry of nitrosonium tetrafluoroborate (215 mg, 1.84 mmol) in methylene chloride (6 mL) cooled to 0°C was treated dropwise with a solution of 2-(3-amino-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionic acid methyl ester (500 mg, 1.54 mmol) in a small amount of methylene chloride. The resulting reaction mixture was stirred at 0°C for 1 h. The reaction mixture was then allowed to warm to 25°C and then treated

## Example 169

## 1-[2-(4-Cyano-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea



5 A solution of (4-bromo-phenyl)-acetic acid (6.77 g, 31.48 mmol) in methanol (32 mL) was treated with a catalytic amount of concentrated sulfuric acid (3 drops). The reaction mixture was then heated to reflux for 24 h. At this time, the reaction was concentrated *in vacuo*. The residue was treated with an aqueous solution of sodium bicarbonate (100 mL). This solution was extracted with ethyl acetate (3 x 100 mL). The organic layers were washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford (4-bromo-phenyl)-acetic acid methyl ester (6.75 g, 94%) as a yellow oil. The product was used without further purification.

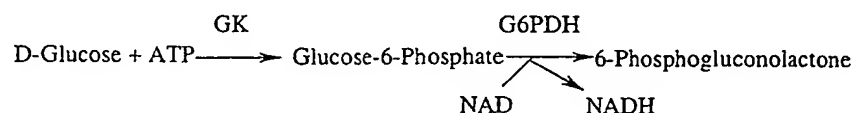
15 A solution of freshly prepared lithium diisopropylamide (50.5 mL of 0.3 M, 15.15 mmol) cooled to -78°C was treated with (4-bromo-phenyl)-acetic acid methyl ester (3.36 g, 14.67 mmol) in tetrahydrofuran/1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (37 mL, 3:1). The resulting solution was stirred at -78°C for 45 min. At this time, the reaction was treated with a solution of iodomethylcyclopentane (3.24 g, 15.45 mmol) in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (3.24 mL). The reaction mixture was stirred at -78°C for 4 h. The reaction was warmed to 25°C and stirred at 25°C for 20 h. The reaction mixture was then quenched by the slow addition of a saturated ammonium chloride solution (40 mL). The reaction mixture was then poured into water (100 mL) and the product was extracted into ethyl acetate (3 x 75 mL). The organics were washed with a saturated aqueous sodium chloride solution (3 x 100 mL) and a saturated aqueous solution of lithium chloride (3 x 100 mL), dried over sodium sulfate and magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60,

20  
25

### Biological Activity Examples

### Example A: *In Vitro* Glucokinase Activity

**Glucokinase Assay:** Glucokinase (GK) was assayed by coupling the production of glucose-6-phosphate to the generation of NADH with glucose-6-phosphate dehydrogenase (G6PDH, 0.75-1 kunits/mg; Boehringer Mannheim, Indianapolis, IN) from *Leuconostoc mesenteroides* as the coupling enzyme (Scheme 2).



Scheme 2

10

Recombinant Human liver GK1 was expressed in *E. coli* as a glutathione S-transferase fusion protein (GST-GK) [Liang et al, 1995] and was purified by chromatography over a glutathione-Sepharose 4B affinity column using the procedure provided by the manufacturer (Amersham Pharmacia Biotech, Piscataway, NJ). Previous studies have demonstrated that the enzymatic properties of native GK and GST-GK are essentially identical (Liang et al, 1995; Neet et al., 1990).

The assay was conducted at 25° C in a flat bottom 96-well tissue culture plate from Costar (Cambridge, MA) with a final incubation volume of 120 µL. The incubation mixture contained: 25 mM Hepes buffer (pH, 7.1), 25 mM KCl, 5 mM D-glucose, 1 mM ATP, 1.8 mM NAD, 2 mM MgCl<sub>2</sub>, 1 µM sorbitol-6-phosphate, 1 mM dithiothreitol, test drug or 10% DMSO, 1.8 unit/ml G6PDH, and GK (see below). All organic reagents were > 98 % pure and were from Boehringer Mannheim with the exceptions of D-glucose and Hepes that were from Sigma Chemical Co, St Louis, MO. Test compounds were dissolved in DMSO and were added to the incubation mixture minus GST-GK in a volume of 12 µl to yield a final DMSO concentration of 10%. This mix was preincubated

**Example B: *In Vivo* Glucokinase Activity****Glucokinase Activator *in vivo* Screen Protocol**

5 C57BL/6J mice are orally dosed via gavage with Glucokinase (GK) activator at 50 mg/kg body weight following a two hour fasting period. Blood glucose determinations are made five times during the six hour post-dose study period.

Mice (n=6) are weighed and fasted for a two hour period prior to oral treatment.

10 GK activators are formulated at 6.76 mg/ml in Gelucire vehicle (Ethanol:Gelucire44/14:PEG400q.s. 4:66:30 v/w/v. Mice are dosed orally with 7.5µL formulation per gram of body weight to equal a 50 mg/kg dose. Immediately prior to dosing, a pre dose (time zero) blood glucose reading is acquired by snipping off a small portion of the animals tail (~1 mm) and collecting 15 µL blood into a heparinized

15 capillary tube for analysis. Following GK activator administration, additional blood glucose readings are taken at 1, 2, 4, and 6 hours post dose from the same tail wound. Results are interpreted by comparing the mean blood glucose values of six vehicle treated mice with six GK activator treated mice over the six hour study duration. Compounds are considered active when they exhibit a statistically significant ( $p \leq 0.05$ ) decrease in blood

20 glucose compared to vehicle for two consecutive assay time points.

-335-

$R^{40}$  is hydrogen, lower alkyl, lower alkenyl, hydroxy lower alkyl, halo lower alkyl,  
- $(CH_2)_n-C(O)OR^5$  or  $-C(O)-(CH_2)_n-C(O)OR^6$ ;

$R^5$  is hydrogen, lower alkyl or perfluoro-lower alkyl;

$R^6$ ,  $R^7$  and  $R^8$  are independently hydrogen or lower alkyl; and

5       $n$  is 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein

10       $R^1$  and  $R^2$  are independently hydrogen, halo, amino, hydroxyamino, cyano, nitro,  
lower alkyl,  $-OR^5$ ,  $-C(O)OR^5$ , perfluoro-lower alkyl, lower alkyl thio, perfluoro-  
lower alkyl thio, lower alkyl sulfonyl, perfluoro-lower alkyl sulfonyl, lower alkyl  
sulfinyl, or sulfonamido;

$R^3$  is cycloalkyl having from 3 to 7 carbon atoms;

15       $R^4$  is an unsubstituted or mono-substituted five- or six-membered heteroaromatic ring  
connected by a ring carbon atom to the amine group shown, which five- or six-  
membered heteroaromatic ring contains from 1 to 3 heteroatoms selected from  
sulfur, oxygen or nitrogen, with one heteroatom being nitrogen which is adjacent  
to the connecting ring carbon atom; said mono-substituted heteroaromatic ring  
being monosubstituted at a position on a ring carbon atom other than adjacent to  
20      said connecting carbon atom with a substituent selected from the group  
consisting of lower alkyl, halo, nitro, cyano,  $-(CH_2)_n-OR^6$ ,  $-(CH_2)_n-C(O)OR^7$ ,  
 $-(CH_2)_n-C(O)NHR^6$ ,  $-C(O)-C(O)OR^8$  or  $-(CH_2)_n-NHR^6$ ;

$n$  is 0, 1, 2, 3 or 4;

$R^5$  is hydrogen, lower alkyl, or perfluoro-lower alkyl; and

25       $R^6$ ,  $R^7$  and  $R^8$  are independently hydrogen or lower alkyl;

or a pharmaceutically acceptable salt thereof.

9. A compound according to any of claims 1 to 8, wherein  $R^2$  is hydrogen, lower alkyl sulfonyl, perfluoro-lower alkyl, perfluoro-lower alkyl sulfonyl, halo or  $-OR^5$  wherein  $R^5$  is perfluoro-lower alkyl.
- 5 10. A compound according to any of claims 1 to 9, wherein  $R^2$  is halo or lower alkyl sulfonyl.
11. A compound according to any of claims 1 to 10, wherein the amide is in the R  
10 configuration at the asymmetric carbon shown.
12. A compound according to any of claims 1 to 11, wherein  $R^3$  is cyclopentyl, cyclohexyl or cycloheptyl.
- 15 13. A compound according to any of claims 1 to 12, wherein  $R^3$  is cyclopentyl.
14. A compound according to any of claims 1 to 13, selected from the group consisting of:
- 20 2-(3-chloro-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide,  
2-(4-bromo-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide,  
2-(4-chloro-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide,  
3-cyclopentyl-2-(3,4-dichlorophenyl)-N-thiazol-2-yl-propionamide,  
3-cyclopentyl-N-thiazol-2-yl-2-(4-trifluoromethyl-phenyl)-propionamide,  
3-cyclopentyl-2-(3-fluoro-4-trifluoromethyl-phenyl)-N-thiazol-2-yl-propionamide,  
3-cyclopentyl-2-(4-fluoro-3-trifluoromethyl-phenyl)-N-thiazol-2-yl-propionamide,  
25 3-cyclopentyl-N-thiazol-2-yl-2-(3-trifluoromethyl-phenyl)-propionamide,  
3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-N-thiazol-2-yl-propionamide,  
3-cyclopentyl-2-(4-nitrophenyl)-N-thiazol-2-yl-propionamide,  
2-(4-amino-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide,  
2-(3-amino-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide,  
30 2-(4-chloro-3-nitro-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide,  
2-(4-cyano-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide,

- 3-cyclopentyl-2-(3-fluoro-4-hydroxy-phenyl)-N-thiazol-2-yl-propionamide,  
3-cyclopentyl-2-(3,4-dichlorophenyl)-N-(5-hydroxymethyl-thiazol-2-yl)-  
propionamide,  
5 3-cyclopentyl-2-(3,4-dichlorophenyl)-N-[4-(2-hydroxyethyl)-thiazol-2-yl]-  
propionamide,  
2-(4-chloro-phenyl)-3-cyclopentyl-N-(5-hydroxymethyl-thiazol-2-yl)-propionamide,  
3-cyclopentyl-2-(3,4-dichlorophenyl)-N-(4-hydroxymethyl-thiazol-2-yl)-  
propionamide,  
10 3-cyclopentyl-N-(4-hydroxymethyl-thiazol-2-yl)-2-(4-methanesulfonyl-phenyl)-  
propionamide,  
3-cyclopentyl-N-[4-(2-hydroxyethyl)-thiazol-2-yl]-2-(4-methanesulfonyl-phenyl)-  
propionamide,  
3-cyclopentyl-2-(3,4-dichlorophenyl)-N-(4-methyl-thiazol-2-yl)-propionamide,  
3-cyclopentyl-2-(3,4-dichlorophenyl)-N-(5-methyl-thiazol-2-yl)-propionamide,  
15 {2-[2-(3-chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazol-4-yl}-acetic acid  
ethyl ester,  
{2-[2-(3-chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazol-4-yl}-acetic acid  
methyl ester,  
20 2-[2-(3-chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazole-4-carboxylic acid  
methyl ester,  
2-[2-(3-chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazole-4-carboxylic acid  
ethyl ester,  
{2-[2-(4-chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazol-4-yl}-acetic acid  
ethyl ester,  
25 2-[2-(4-chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazole-4-carboxylic acid  
methyl ester,  
2-[2-(4-chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazole-4-carboxylic acid  
ethyl ester,  
30 {2-[2-(4-chloro-phenyl)-3-cyclopentyl-propionylamino]-thiazol-4-yl}-acetic acid  
methyl ester,  
{2-[3-cyclopentyl-2-(3,4-dichlorophenyl)-propionylamino]-thiazol-4-yl}-acetic  
acid,  
{2-[3-cyclopentyl-2-(3,4-dichlorophenyl)-propionylamino]-thiazol-4-yl}-acetic acid  
ethyl ester,  
35 2-[3-cyclopentyl-2-(3,4-dichlorophenyl)-propionylamino]-thiazole-5-carboxylic  
acid,

- 3-cyclopentyl-2-(3,4-dichlorophenyl)-N-(5-nitro-thiazol-2-yl)-propionamide,  
3-cyclopentyl-2-(3-fluoro-4-trifluoromethyl-phenyl)-N-pyridin-2-yl-propionamide,  
3-cyclopentyl-2-(3,4-dichloro-phenyl)-N-pyridin-2-yl-propionamide,  
3-cyclopentyl-N-pyridin-2-yl-2-(4-trifluoromethyl-phenyl)-2-propionamide,  
5 3-cyclopentyl-N-thiazol-2-yl-2-(3-trifluoromethyl-phenyl)-propionamide,  
2-(3-chloro-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide,  
2-(4-amino-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide,  
2-(4-cyano-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide,  
2-(4-chloro-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide,  
10 2-(4-chloro-3-nitro-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide,  
3-cyclopentyl-2-(4-nitro-phenyl)-N-pyridin-2-yl-propionamide,  
2-(4-cyano-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide,  
3-cyclopentyl-2-(4-methylsulfonyl-phenyl)-N-pyridin-2-yl-propionamide,  
3-cyclopentyl-N-pyridin-2-yl-2-(4-trifluoromethylsulfonyl-phenyl)-propionamide,  
15 3-cyclopentyl-2-(4-methanesulfonyl-3-nitrophenyl)-N-pyridin-2-yl-propionamide,  
3-cyclopentyl-2-(4-methanesulfonyl-phenyl)-N-pyridin-2-yl-propionamide,  
2-(3-bromo-4-methanesulfonyl-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide,  
2-(3-cyano-4-methanesulfonyl-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide,  
20 3-cyclopentyl-2-(4-ethanesulfonyl-phenyl)-N-pyridin-2-yl-propionamide,  
2-(3,4-bis-methanesulfonyl-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide,  
2-(3-chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-N-pyridin-2-yl-propionamide,  
25 3-cyclopentyl-2-(4-methanesulfonyl-3-trifluoromethyl-phenyl)-N-pyridin-2-yl-propionamide,  
3-cyclopentyl-N-pyridin-2-yl-2-(4-trifluoromethanesulfonyl-phenyl)-propionamide,  
3-cyclopentyl-2-(3,4-dichloro-phenyl)-N-(5-carboxymethylpyridin)-2-yl-propionamide,  
30 6-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionylamino]-nicotinic acid methyl ester,  
6-[2-(4-chloro-phenyl)-3-cyclopentyl-propionylamino]-nicotinic acid,  
6-[2-(3-chloro-phenyl)-3-cyclopentyl-propionylamino]-nicotinic acid methyl ester,  
6-[2-(4-chloro-phenyl)-3-cyclopentyl-propionylamino]-nicotinic acid methyl ester,



- 3-cyclopentyl-2-(3,4-dichloro-phenyl)-N-(5-nitropyridin)-2-yl-propionamide,  
 3-cyclopentyl-2-(3,4-dichloro-phenyl)-N-(5-methylpyridin)-2-yl-propionamide,  
 3-cyclopentyl-2-(3,4-dichloro-phenyl)-N-(4-methylpyridin)-2-yl-propionamide,  
 3-cyclopentyl-2-(3,4-dichloro-phenyl)-N-(6-methylpyridin)-2-yl-propionamide,  
 5 3-cyclopentyl-N-(5-methyl-pyridin-2-yl)-2-(4-trifluoromethanesulfonyl-phenyl)-  
 propionamide,  
 3-cyclopentyl-2-(4-fluoro-3-trifluoromethyl-phenyl)-N-(5-methyl-pyridin-2-yl)-  
 propionamide,  
 6-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionylamino]-N-methyl-nicotinamide,  
 10 3-cyclopentyl-2-(3,4-dichlorophenyl)-N-(1H-imidazol-2-yl)-propionamide,  
 3-cyclopentyl-2-(3,4-dichlorophenyl)-N-(5-methyl-isoxazol-3-yl)-propionamide,  
 3-cyclopentyl-2-(3,4-dichlorophenyl)-N-oxazol-2-yl-propionamide,  
 3-cyclopentyl-2-(3,4-dichlorophenyl)-N-pyridazin-3-yl-propionamide,  
 3-cyclopentyl-2-(3,4-dichlorophenyl)-N-pyrimidin-2-yl-propionamide,  
 15 3-cyclopentyl-2-(3,4-dichlorophenyl)-N-pyrimidin-6-yl-propionamide,  
 3-cyclopentyl-2-(4-nitro-phenyl)-N-pyrimidin-4-yl-propionamide,  
 3-cyclopentyl-2-(3,4-dichlorophenyl)-N-[1,3,4]thiadiazol-2-yl-propionamide,  
 2-[4-methanesulfonyl phenyl]-3-cyclohexyl N-thiazol-2-yl-propionamide, and  
 2-[4-methanesulfonyl phenyl]-3-cycloheptyl N-thiazol-2-yl-propionamide.  
 20
15. A compound according to any of claims 1 to 13, selected from the group consisting of:
- 1-(3-cyclopentyl-2-phenyl-propionyl)-3-methyl-urea,  
 1-[2-(3-chloro-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea,  
 1-[2-(4-chloro-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea,  
 25 1-[2-(4-cyano-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea,  
 1-[2-(4-bromo-phenyl)-3-cyclopentyl-propionyl]-3-methyl urea,  
 [3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-urea,  
 1-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-methyl-urea,  
 1-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionyl]-3-ethyl-urea,  
 30 1-allyl-3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-urea,  
 1-allyl-3-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionyl]-urea,  
 1-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-ethyl-urea,

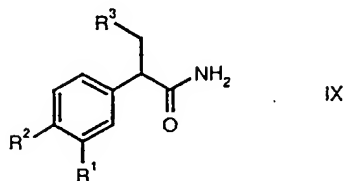
-345-

- 3-[cyclohexyl-2-(3,4-dichloro-phenyl)-propionyl]-urea,  
[3-cyclohexyl-2-(3,4-dichloro-phenyl)-propionyl]-3-methyl-urea,  
[3-cycloheptyl-2-(3,4-dichloro-phenyl)-propionyl]-urea,  
3-{3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido}-propionic acid  
5 ethyl ester,  
{3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido}-acetic acid ethyl  
ester,  
{3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido}-acetic acid methyl  
ester,  
10 3-{3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido}-propionic acid  
methyl ester,  
{3-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionyl]-ureido}-acetic acid ethyl  
ester,  
3-{3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-ureido}-3-oxo-propionic  
15 acid ethyl ester,  
1-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-(2-hydroxy-ethyl)-urea,  
1-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-(2-hydroxy-propyl)-urea,  
1-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-(3-hydroxy-propyl)-urea,  
1-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionyl]-3-(2-hydroxy-propyl)-urea,  
20 1-(2-chloro-ethyl)-3-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-urea, and  
1-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionyl]-3-(3-hydroxy-propyl)-urea.
16. A compound according to any of claims 1 to 14, selected from the group consisting of:
- 3-Cyclopentyl-2-(4-methanesulfonyl-phenyl)-N-thiazol-2-yl-propionamide,  
25 3-Cyclopentyl-N-thiazol-2-yl-2-(4-trifluoromethoxy-phenyl)-propionamide,  
3-Cyclopentyl-N-thiazol-2-yl-2-(4-trifluoromethanesulfonyl-phenyl)-propionamide,  
3-Cyclopentyl-2(R)-(3,4-dichloro-phenyl)-N-pyridin-2-yl-propionamide,  
6-[3-Cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionylamino]-nicotinic acid  
methyl ester,  
30 N-(5-Chloro-pyridin-2-yl)-3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionamide,  
3-Cyclopentyl-N-pyridin-2-yl-2-(4-trifluoromethanesulfonyl-phenyl)-propionamide,  
3-Cyclopentyl-N-(5-methyl-pyridin-2-yl)-2-(4-trifluoromethanesulfonyl-phenyl)-  
propionamide,  
35 3-Cyclopentyl-2(R)-(3,4-dichloro-phenyl)-N-(5-hydroxymethyl-pyridin-2-yl)  
propionamide,

17. A compound according to any of claims 1 to 13 and 15, selected from the group consisting of:
- 1-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionyl]-3-ethyl-urea,
  - 5 1-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionyl]-3-methyl-urea,
  - 1-[3-cyclopentyl-2-(3,4-dichloro-phenyl)-propionyl]-3-methyl urea,
  - 1-[3-cyclopentyl-2-(4-methanesulfonyl-phenyl)-propionyl]-3-methyl urea,
  - 1-Allyl-3-[3-cyclopentyl-2(R)-(3,4-dichloro-phenyl)-propionyl]-urea,
  - 1-[2-(3-Chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea,
  - 10 1-[2(R)-(3-Chloro-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea, and
  - 1-[2-(3-Bromo-4-methanesulfonyl-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea.
18. The use of the compounds according to any of claims 1 to 17 for the treatment of type  
15 II diabetes.
19. A pharmaceutical composition comprising a compound of any of claims 1 to 17 and a pharmaceutically acceptable carrier and/or adjuvant.
- 20 20. The use of a compound according to any of claims 1 to 17 for the preparation of medicaments containing a compound according to any of claims 1 to 17 for the treatment or prophylaxis of type II diabetes.
21. A method for the prophylactic or therapeutic treatment of type II diabetes, which  
25 method comprises administering a compound of any of claims 1 to 17 to a human being or an animal.
22. A process for the preparation of the compounds of formula I according to any of claims 1 to 17, which process comprises:

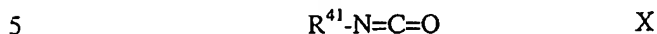
-349-

(b) The reaction of a compound of formula IX:



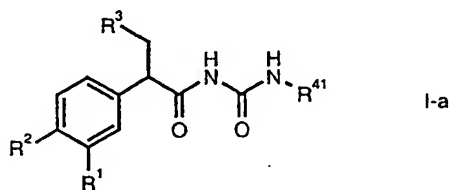
wherein  $R^1$ ,  $R^3$  and  $R^3$  are as defined in claim 1;

with a compound of the formula X:



wherein  $R^{41}$  is lower alkyl, lower alkenyl, hydroxy lower alkyl, halo lower alkyl or  $-(CH_2)_n-C(O)OR^5$ , wherein  $R^5$  is hydrogen or lower alkyl and  $n$  is as defined above;

to produce a compound of formula I-a:

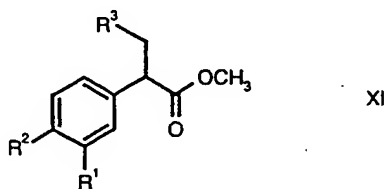


10

wherein  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^{41}$  are as defined above;

optionally followed by the conversion of one or both of the substituents  $R^1$  and/or  $R^2$  into another substituent  $R^1$  and/or  $R^2$  as defined in claim 1.

15 (c) The reaction of a compound of the formula XI:



wherein  $R^1$ ,  $R^2$  and  $R^3$  are as defined in claim 1;

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optionally followed by the conversion of one or both of the substituents  $R^1$  and/or  $R^2$  into another substituent  $R^1$  and/or  $R^2$  as defined in claim 1.

23. The invention as described hereinbefore.

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/02450

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D277/46 A61K31/426 C07D277/56 C07D213/75 C07D213/80  
C07D213/82 C07D213/85 C07D233/88 C07D237/20 C07D239/42  
C07D241/20 C07D253/06 C07D261/14 C07D263/48 C07D285/12

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, EPO-Internal, PAJ, BIOSIS, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 249 241 C (BAYER) 13 July 1912 (1912-07-13) see example 1 page 1, right-hand column, line 46 - line 50; claim 1	1,5
X	SPIELMAN M. A. ET AL.: "Anticonvulsant Drugs. II. Some Acylureas" JOURNAL OF AMERICAN CHEMICAL SOCIETY, vol. 70, 1948, pages 4189-4191, XP000940775 page 4190; table 1	1,5
A	US 3 776 917 A (MANN T ET AL) 4 December 1973 (1973-12-04) column 1, line 23 - line 60 column 6, line 31 - line 57	1-22

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

\*A\* document defining the general state of the art which is not considered to be of particular relevance

\*E\* earlier document but published on or after the international filing date

\*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

\*O\* document referring to an oral disclosure, use, exhibition or other means

\*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*Z\* document member of the same patent family

Date of the actual completion of the international search

13 October 2000

Date of mailing of the international search report

26.10.00

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentaan 2  
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Authorized officer

Schmid, J-C

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP 00/02450

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claims 18 and 21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 23  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
The scope of claim 23 is unclear
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/EP 00/02450

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 249241 C		NONE	
US 3776917 A	04-12-1973	NONE	

3229  
379  
622  
81